The Collection and Reporting of Adverse Events in Randomized Controlled Trials: Gabapentin for Neuropathic Pain and Quetiapine for Bipolar Depression as Case Examples

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Abstract

Background

Healthcare stakeholders need access to the evidence about the adverse events (AEs) of health interventions to make informed clinical decisions. This dissertation addresses research gaps in the collection and reporting of AEs in randomized controlled trials (RCTs).

Methods

We examined sources about RCTs of gabapentin for neuropathic pain and quetiapine for bipolar depression ("eligible" RCTs). We identified public sources (e.g., journal articles) and non-public sources (e.g., clinical study reports) available by March 2015 (gabapentin) and January 2015 (quetiapine). We extracted data about non-systematic (e.g., unsolicited by investigators) and systematic (e.g., collected using questionnaires) AEs, including "serious" AEs (defined by the Food and Drug Administration). We compared reporting of non-systematic (Aim 1) and systematic (Aim 2) AEs in public and non-public sources. We assessed whether AEs were "meta-analyzable" (i.e., we could calculate between-group effects) and whether systematic AE outcomes were "fully-defined" (i.e., specified all five elements of an outcome). In Aim 3, we extracted and compared "selection criteria" (i.e., reported methods for selecting which non-systematic AEs to report) and assessed the impact of selection criteria on reporting of individual RCTs and meta-analyses of reported data.

Results

We identified 21 gabapentin RCTs and 7 quetiapine RCTs. In Aim 1, the majority of non-systematic AEs were reported only in non-public sources for gabapentin (341/419 [81%]) and quetiapine (436/471 [93%]). Most serious non-systematic AEs were reported only in non-public sources: 56/72 (78%) and 39/46 (85%) for gabapentin and quetiapine. Gabapentin RCTs did not report any systematic AEs, so Aim 2 is based on only quetiapine RCTs. About half (90/159; 57%) of all results in public sources were both associated with defined outcomes and meta-analyzable, compared with nearly all (610/636; 96%) results in non-public sources. In Aim 3, all selection criteria we identified were based on a numerical threshold for reporting (e.g., ≥5%). Choice of selection criteria had a large impact on both the AEs reported in individual RCTs and meta-analysis results.

Conclusions

Poor reporting of non-systematic and systematic AEs has consequences for healthcare stakeholders. Without open access to non-public sources, healthcare decisions are based on only a subset of the evidence about AEs.

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understanding have gotten me through the pressures and stress that come with both doctoral programs and life.

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List of Abbreviations

AE	adverse event
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
CSR	clinical study report
CSR-S	clinical study report-synopsis
EMA	European Medicines Agency
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform Search Portal
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPD	individual participant data
IQWiG	Institute for Quality and Efficiency in Health Care
LDL	low-density lipoprotein
MA	meta-analyzable
MUDS	Multiple Data Sources
NA	not applicable
NIH	National Institute of Health
PCORI	Patient-Centered Outcomes Research Institute

RCT	randomized controlled trials
RD	risk difference
SAS	Simpson-Angus Scale
SMD	standardized mean difference
SRDR	Systematic Review Data Repository
SSRI	selective serotonin reuptake inhibitor
YMRS	Young Mania Rating Scale

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Chapter 1. Introduction

Background

Adverse events (AEs) are an important consideration in patient-centered research, as indicated by the priorities of the National Academy of Medicine (1), the Patient-Centered Outcomes Research Institute (PCORI) (2), and the United States Department of Health and Human Services (3). AEs are also important to regulators, who determine whether the potential benefits of an intervention outweigh the potential AEs for products being considered for indication approval (4). Regulatory approval is typically based on the results of randomized controlled trials (RCTs) (4). This dissertation is focused on the collection and reporting of AEs in RCTs.

Methods for collecting and classifying adverse events

During an RCT, AEs can be collected using two main methods. "Non-systematic AEs" are either reported by patients without being solicited by trial investigators or solicited using broad, open-ended questions such as, "have you noticed any changes since your last visit?" (5, 6). Non-systematic AEs are collected as free-text that describes participant experiences (5, 6). Free-text responses are consolidated and coded to facilitate analysis (7). For example, two participants might experience similar AEs, but use different wording to describe them (e.g., head pain vs. headache). To facilitate analysis, these two different descriptions would be coded as the same AE (8-10). Although the goal of coding non-systematic AEs for analysis is to standardize data within and across trials, this can prove challenging; even experienced coders may code the same free-text as different AEs (7). Challenges related to coding non-systematic AEs may

lead to inconsistency both within and across trials, which may complicate comparison of the safety of different interventions (7).

When AEs are suspected of being related to the intervention, they might be collected systematically ("systematic AEs"). Systematic AEs are collected and recorded in the same manner for each participant at pre-specified intervals using methods of ascertainment that are related to specific AEs (5, 6). Some examples of systematic collection methods are laboratory tests (e.g., blood glucose), vital signs (e.g., blood pressure), questionnaires (e.g., the Young Mania Rating Scale), and checklists. Systematic AEs can be described using a framework that includes five elements of an outcome: (1) domain (e.g., mania); (2) specific measurement (e.g., Young Mania Rating Scale); (3) metric (e.g., a participant's change in Young Mania Rating Scale from baseline); (4) method of data aggregation for analysis (e.g., mean Young Mania Rating Scale score, proportion of participants reaching a particular threshold); and (5) time-point at which the outcome was assessed (11, 12). An outcome would be considered "fully-defined" if all five elements of the outcome were clearly specified. For example, "mania symptoms as assessed by the mean change from baseline to eight weeks using the Young Mania Rating Scale" would be considered fully-defined; "mania symptoms assessed using the Young Mania Rating Scale" would not be considered fully-defined because it is missing the metric, method of aggregation, and time-point. According to the FDA, "[p]otential problems that may be suspected because of preclinical data or because of effects of related drugs should be targeted for evaluation" (13).

It is important to distinguish between these two methods of AE data collection. Evidence suggests that when investigators use different methods to collect AEs (i.e., systematic vs. non-systematic), different proportions of patients may report experiencing AEs (14-18). For example, one RCT randomized participants to different methods of AE data collection and found that participants who were asked to use a checklist reported about 20 times more AEs than participants who were asked an open-ended question (15). Other evidence suggests that the proportion of patients reporting sexual side effects from selective serotonin reuptake inhibitors (SSRIs, a class of anti-depressants) ranges from 2% to 73%, and that this variation arises largely from whether AEs were collected using non-systematic or systematic methods (18). The difference in the proportion of participants reporting AEs makes it difficult to both synthesize information from multiple trials about the same intervention and condition and compare different interventions for the same condition.

Both non-systematic and systematic AEs can be classified as "serious." Serious AEs are categorized as such by trial investigators, typically based on definitions determined by regulatory agencies. The FDA defines serious AEs as "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (19, 20). The European Medicines Agency (EMA) uses a comparable definition (21).

Consistency of adverse event collection across trials

During the process of designing an RCT, investigators must select which outcomes they are interested in collecting, analyzing, and reporting. During this process, investigators must determine not only *which* outcome domains (e.g., depression, mania) to collect, but also *how* they will collect data about each outcome domain. When there are multiple options, selecting an instrument to use for data collection can prove challenging. For example, there are hundreds of different scales that measure psychiatric symptoms (22). When there are this many different ways to assess each outcome domain, trial investigators may understandably choose to collect different fully-defined outcomes even when they identify the same outcome domains as important for collection. Inconsistent collection of outcomes across RCTs complicates synthesizing data from multiple RCTs about the same intervention and condition or comparing the relative effectiveness and safety of different interventions for the same condition.

To increase consistency of outcomes across RCTs, there has been increased research related to developing "core outcome sets," which are "an agreed minimum set of outcomes" to be collected during studies about the same condition (23, 24). Established methods for developing core outcomes sets vary widely and may include the Delphi Technique, surveys, semi-structured discussion, and unstructured group discussion, among others (25). The stakeholders involved in developing core outcome sets also vary, sometimes including clinical experts, patients or patient representatives,

non-clinical research experts (e.g., statisticians, epidemiologists), regulatory agencies, policy-makers, journal editors, and others (25). The Core Outcome Measures in Effectiveness Trials (COMET) Initiative seeks to standardize methods for developing core outcome sets and compile a searchable database of completed and ongoing core outcome sets (23).

Current core outcome sets are typically focused on outcomes to be collected in studies related to a particular condition (24) to facilitate comparison of different interventions for the same condition. It may be inappropriate, however, to collect the same AEs for all interventions for a particular condition; different types of interventions may have different expected AEs. For example, bipolar depression can be treated using both pharmaceutical interventions (e.g., quetiapine) and behavioral interventions (e.g., cognitive behavioral therapy). These two types of interventions are likely to have very different expected AEs, so it may be inappropriate to collect data about the same AEs. Therefore, it may be better to develop core outcome sets of AEs that are specific to types of interventions (e.g., drug class). For example, it would be important to be able to compare the relative weight gain that participants experience on different types of atypical anti-psychotics. In some cases, it might even be appropriate to examine the same AEs across different conditions. For example, quetiapine is approved for use in patients with schizophrenia, as well as bipolar disorder; the FDA approved label for quetiapine includes many of the same AEs for both conditions (26).

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has developed a suggested core outcome set for studies that are assessing chronic pain conditions (27). This core outcome set makes recommendations for several effectiveness outcome domains that should be collected, as well as which measurement tools should be used to collect each of these effectiveness outcome domains. However, the core outcome set does not make specific recommendations related to the collection of AEs. Instead, they recommend collecting "symptoms and adverse events" (27). Although the report states that systematic methods of collecting AEs are often more sensitive and provide more informative than non-systematic methods, it provides little guidance as to which AEs should be collected systematically or what measurement tools should be used. Because both effectiveness and AE outcomes are important and AE outcomes may be underdeveloped in current core outcome sets, it might be appropriate to have two separate core outcome sets for effectiveness and AE outcomes.

Potential sources of data about adverse events

After data are collected during RCTs, these data must be analyzed and reported. We have developed a theoretical framework to describe the different sources of RCT data about AEs and how these different sources of evidence may contribute to systematic reviews and meta-analyses, which combine data from multiple studies to calculate a summary effect estimate (Figure 1-1). When an RCT is conducted, data are recorded on case report forms. These data are then entered into a database, making up the IPD. The data are then analyzed and reported in a variety of sources: conference

abstracts, journal articles, clinical trial registries such as ClinicalTrials.gov, and, when the RCT is conducted by a pharmaceutical company for regulatory approval, CSRs and CSR-Synopses. CSRs and sometimes IPD are submitted to regulatory agencies, such as the FDA, for drug approval. The FDA reviews the submitted data and creates its own reports. The FDA also works with the company to create and approve a label for the medication.

Systematic reviewers can then use a mix of sources (abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD) to perform meta-analyses. We have classified these sources as either public (i.e., abstracts, journal articles, clinical trial registries, and FDA reviews) or non-public (i.e., CSRs, CSR-Synopses, and IPD). Healthcare stakeholders interested in AEs often have access to only some of these sources, with very little guidance regarding their reliability and completeness. In this dissertation, we aim to explore how the use of different sources and different methods of reporting affect the conclusions regarding safety, using gabapentin for neuropathic pain and quetiapine for bipolar depression as case examples.

Completeness and accuracy of adverse event reporting in different sources

Despite the importance of safety, several studies have shown that harms are poorly reported in publications of RCTs covering a variety of medical disciplines (28-35). The quality of reporting is typically assessed by describing what information is and is not available in published literature. Some items that should be reported are collection methods, results of AEs reported by intervention group, and clear statistical methods

(36). A systematic survey of RCTs in 2001 showed that 14% of trials did not mention safety at all, while another 32% either did not report results by arm or made only general statements (32). Despite the introduction of reporting guidelines (36), reporting has not improved significantly (33-35, 37).

There has also been research comparing what data are available in different sources. Hartung et al compared AEs reported in a random sample of trials on ClinicalTrials.gov to those reported in publications. Discrepancies between the two sources were common, but there was no way of determining which source was more accurate without additional information (38). Other evidence suggests that trial registries may contain more information about AEs than journal articles (39-41).

CSRs represent an important source of data about AEs. CSRs are comprehensive documents created by pharmaceutical companies for submission to regulatory agencies detailing the design, methods, analyses, and results of a single study (42). CSRs are then submitted to regulatory agencies to obtain approval for medications. In 1995, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) proposed guidelines for the structure and content of CSRs. The purpose of these guidelines was to "assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review" (42). CSRs should include detailed descriptions of study design, patient characteristics, analysis methods, aggregate data for effectiveness outcomes and all AEs,

and individual patient data listings. CSRs are often thousands of pages in length and represent a largely untapped source of unpublished data (43, 44).

The benefit of using CSRs in systematic reviews and meta-analyses was clearly demonstrated in the case of neuraminidase inhibitors (Tamiflu®). Conclusions regarding effectiveness changed when data from CSRs were included in the systematic review. There were also data in the CSRs about serious AEs that occurred in trials but were never reported in journal articles (45, 46). Other studies have compared CSRs with journal articles and found that much of the information in CSRs is not reported in journal articles (47, 48). One study compared AE reporting in CSRs, trial registries, and journal publications; CSRs were more complete than either trial registries or journal publications (49).

Another source that is typically unavailable to the public is IPD. Because CSRs are produced only by pharmaceutical companies, IPD may provide access to typically unpublished data for non-industry trials. In one case study, Rodgers et al compared IPD with journal articles. They found that only 19.0% of AEs in the IPD were reported in journal articles (50).

Filled out individual case report forms (forms used to collect data) represent another source of data. One case study (48) showed the benefit of using case report forms in a reanalysis of an RCT comparing paroxetine and imipramine to placebo. The data from a selection of case report forms (for 93/275 patients [34%]) was compared to

both the CSR and the full publication. The results were concerning, particularly regarding AEs. For example, 159 AEs were recorded on the case report forms for patients in the paroxetine group, but only 136 AEs were recorded in the CSR. Although CSRs may be more comprehensive than some other sources of data, we must keep in mind that they do not necessarily represent a complete picture.

Although there has been increasing research about the reporting of AEs in different data sources, there are some limitations to the current body of evidence. First, the vast majority of this research compares only two or three different data sources (e.g., journal articles vs. clinical trial registries). Without comparing all available types of sources, it is difficult to speak to the relative accuracy and completeness of different sources or provide guidance for their use in systematic reviews of AEs. In addition, the current research focuses almost exclusively on non-systematic AE reporting.

Reporting bias

After RCTs are conducted, their findings must be disseminated so that healthcare stakeholders can base their clinical decisions on the entire body of evidence; under-reporting of research results has been classified by many as scientific misconduct (51-53). People who volunteer to participate in RCTs do so with the understanding that their contribution will advance the field of medicine (53-55). Under-reporting the results of that research limits the advancement of science, so investigators have an obligation to fully report their results to avoid violating the agreement made with clinical trial participants.

RCTs may not be published (56-58) or reporting may be incomplete (58-63), however. For example, some outcomes may be reported while other outcomes remain unpublished. The Cochrane Handbook defines outcome reporting bias as "selective reporting of some outcomes but not others, depending on the nature and direction of the results" (64). Using quantitative results as a basis for determining reporting can impact the findings of systematic reviews and meta-analyses based on reported results (65-68). The presence of outcome reporting bias has been well-established for effectiveness outcomes (58-63). Although there is evidence that not all AEs are reported (38-40, 47-50, 69), little research has focused on how reported AEs are selected for reporting. The only guideline we have been able to identify related to selecting AEs for reporting is the Final Rule, which describes reporting requirements for ClinicalTrials.gov (5). The Final Rule states that non-systematic AEs that occurred in at least 5% of participants in any intervention group should be reported on ClinicalTrials.gov. The Final Rule also requires that all serious AEs be reported on ClinicalTrials.gov. We have been unable to identify any other research related to how AEs are selected for reporting.

In addition to reporting only selected outcomes, sources may report incomplete information about an outcome. The Institute for Quality and Efficiency in Health Care (IQWiG) assessed outcomes reported in journal articles, trial registrations, and CSRs for completeness of reporting (70). An outcome was considered incompletely reported if results were not reported in enough detail to be included in a meta-analysis. For example, a continuous outcome that reported the mean but no measure of variance

(e.g., confidence interval, standard error) would be considered incompletely reported. Similarly, a dichotomous outcome that reported the number of participants experiencing the AE (i.e., numerator), but not the total number of participants in the analysis (i.e., denominator) would be considered incompletely reported. Across all eligible trials in this study, 86% of outcomes were completely reported in CSRs, compared with 23% in journal articles and 22% in trial registrations (70). Incomplete reporting is problematic for systematic reviewers and meta-analysts, as well as other healthcare stakeholders who based their decisions on the results of systematic reviews. In one study, 55% of reviews were not able to include all eligible trials in the meta-analysis of the review primary outcome (66). When outcomes are reported incompletely and cannot be included in meta-analyses, the summary effect estimates are not based on the entirety of the evidence.

It has also been shown that journal articles about RCTs testing gabapentin for neuropathic pain report incomplete or different outcomes compared with CSRs (71). Primary outcomes (as defined in protocols) were unpublished or changed to secondary outcomes, secondary outcomes (as defined in protocols) were changed to primary outcomes for publication, and new primary outcomes were introduced in publications. Because reporting has been shown to be a problem for the effectiveness data, we believe it is important to investigate the potential for reporting bias in AEs.

Systematic reviews and meta-analyses of adverse events

Although regulatory approval of drugs and biologics is typically based on the results of RCTs (4), RCTs are often not powered to detect differences in the frequency of AEs between interventions (72), because AEs are often rare. Systematic reviews and meta-analyses provide the opportunity to combine data about AEs from multiple RCTs. This may allow the detection of significant differences not identified in individual RCTs because combining data from several RCTs increases the power to detect differences (73).

Systematic reviews and meta-analyses are crucial tools for collecting and combining the data that helps patients and clinicians make medical decisions. To help patients to make informed decisions regarding their medical care, it is important for them to have evidence about potential benefits as well as potential harms. Although systematic reviews focusing on AEs are becoming more common, they are still in the minority (29, 74-76).

Systematic reviews of AEs usually do not include unpublished data (77). Data sharing is one method being used to combat the poor reporting of AEs. Data can be shared in many ways: on clinical trial registries (e.g., ClinicalTrials.gov, International Clinical Trials Registry Platform); directly with other investigators who request data (e.g., systematic reviewers who contact authors of journal articles directly to request data); on a public portal (e.g., ClinicalStudyDataRequest.com (78)); or on a private server or website. There are limitations to current data-sharing efforts, however. Even though

medications that are currently being prescribed were approved many years ago, many data sharing policies exclude data from older "legacy" trials. For example, the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration for publication in 2005 (79). Similarly, ClinicalTrials.gov requires the registration of trials completed after 2007 (80). In addition, data-sharing policies on ClinicalStudyDataRequest.com vary by sponsor, but most require that trials were completed 2010 or later (78). This means that the reporting of AEs in publicly available sources (e.g., journal articles) becomes vitally important.

Systematic reviews and meta-analyses can use data from a variety of sources: abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, and IPD. Many systematic reviews include only journal articles. The Cochrane Handbook recommends searching for conference abstracts and unpublished literature (64). However, there is very little guidance on which sources to use when multiple sources offer different information.

Objective and specific aims of this dissertation

The overall objective of this dissertation is to address important research gaps related to the reporting of both non-systematic and systematic AEs and the potential for outcome reporting bias in non-systematic AEs. We have therefore described three aims below:

- Aim 1: Using RCTs examining gabapentin for neuropathic pain or quetiapine for bipolar depression, (a) compare the reporting of non-systematic AEs across all available sources (i.e., abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD) about RCTs and (b) assess how reporting patterns affect which evidence meta-analyses would be based on.
- Aim 2: Using RCTs examining quetiapine for bipolar depression, (a) compare the reporting of systematic AEs across all available sources (i.e., abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD) about RCTs, (b) describe the completeness of reporting for systematic AEs in each data sources, and (c) assess how reporting patterns affect which evidence meta-analyses would be based on.
- Aim 3: Using RCTs examining gabapentin for neuropathic pain or quetiapine for bipolar depression, (a) compare reported methods for selecting which non-systematic AEs to report both across multiple trials and across multiple sources for the same trial, (b) compare the non-systematic AEs reported in different sources that report using the same methods for selecting AEs for reporting, and (c) use simulated data to assess how using different "selection criteria" impacts the results of meta-analyses.

Detailed methods and results for each of these aims are reported in the following three chapters of this dissertation.

Datasets used in this dissertation

This dissertation was conducted as a sub-study of the Multiple Data Sources (MUDS) study (81). All of the aims of this dissertation used data collected as part of the MUDS study. The aim of the MUDS study was to compare the reporting of RCTs in public and non-public sources, using gabapentin for neuropathic pain and quetiapine for bipolar depression as case examples. These two case examples were selected for several reasons. Both medications are very commonly used for the respective indications; this increases the clinical importance of the results. Originally, gabapentin was approved as a treatment for epilepsy, and has since been approved by the FDA for use in post-herpetic neuralgia; therefore, gabapentin is prescribed off-label for most neuropathic pain conditions. In contrast, quetiapine has been approved for multiple psychiatric conditions, including bipolar depression, so quetiapine is prescribed on-label (i.e., approved by the FDA for use in this indication). Gabapentin was also developed and approved by the FDA earlier than the quetiapine trials, and before many of the relevant policies about trial registration were in place. We did not expect most gabapentin trials to be registered, but we did expect many of the quetiapine trials to be registered. Having our case examples differ in these ways may help us to draw conclusions about RCTs more broadly. In addition, there is evidence of reporting bias related to both gabapentin and quetiapine (71, 82).

We systematically searched PubMed, Embase, Lilacs, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Central Register of

Controlled Trials (CENTRAL) for sources about gabapentin and quetiapine, as well as PsycInfo for sources about quetiapine, without language or date restrictions on March 2, 2015 (gabapentin) and January 26, 2015 (quetiapine). We also searched certain conference proceedings and years for gabapentin trials (81). We searched the International Clinical Trials Registry Platform Search Portal (ICTRP) and the National Institute of Health (NIH) clinical trial registration platform (ClinicalTrials.gov) for trial registrations and associated results related to gabapentin or quetiapine on October 10, 2014. We identified medical and statistical reviews of gabapentin for neuropathic pain and quetiapine for bipolar depression on the FDA website. We obtained non-public sources about gabapentin for neuropathic pain from unsealed litigation. We searched online (http://psychrights.org/) for typically non-public sources about quetiapine for bipolar depression. We requested additional non-public sources in the form of internal company documents from the manufacturers of gabapentin and quetiapine (Pfizer and AstraZeneca, respectively).

The MUDS study identified 80 sources about 21 gabapentin trials and 52 sources about 7 quetiapine trials. For each source, we extracted extensive information that comprised the datasets used for this dissertation. Extracted data included information about baseline participant characteristics (e.g., sex, age, condition), interventions, duration of follow-up, trial funding, financial interests of the authors, effectiveness outcomes, AEs, and quantitative results for both effectiveness outcomes and AEs. Data

extractors also assessed the risk of bias for each source, using the Cochrane risk of bias tool (64). This dissertation focused solely on data related to AEs.

Significance

In order to make informed decisions regarding medical treatment, patients and clinicians need comprehensive and accurate information about the potential benefits and AEs of each intervention. RCTs provide a large amount of data that can be used to aid in decision making. Often, these data from RCTs are distilled into information in the form of systematic reviews and meta-analyses to facilitate easier consumption by clinicians, guideline developers, and other healthcare stakeholders (83).

This doctoral dissertation aims to broaden the knowledge base about how AEs are collected and reported in RCTs, using gabapentin for neuropathic pain and quetiapine for bipolar depression as case examples.

There has been research assessing reporting in different data sources covering a variety of comparisons: conference abstracts and journal articles (57, 84); conference abstracts and trial registries (85); trial registries and journal articles (38-41); CSRs and journal articles (47-49, 71, 86); and IPD and journal articles (48, 50, 87). However, only a subset of this research has been focused on AEs (38-41, 47-50), and nearly all AE research has focused on non-systematic AEs rather than systematic AEs. In addition, most studies compared only two different sources (e.g., journal articles vs. CSRs).

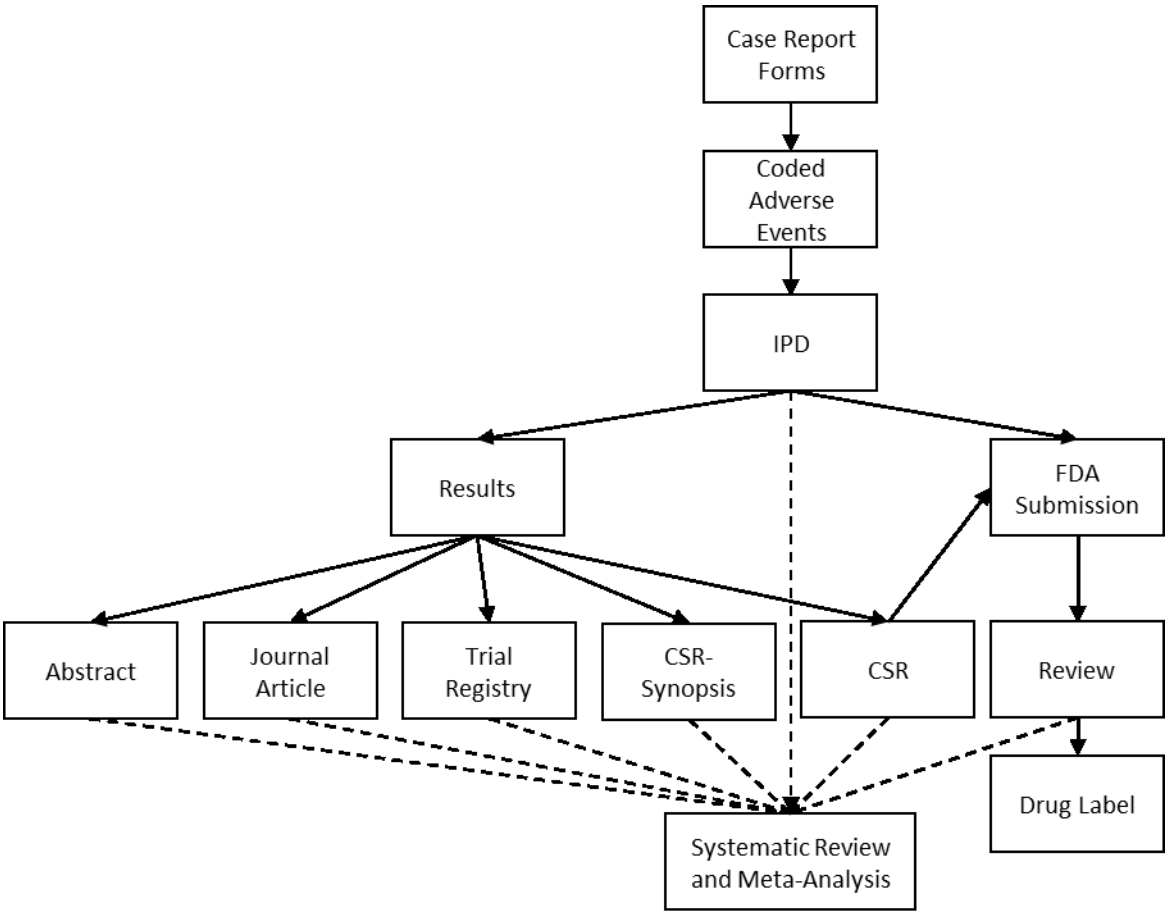
Aim 1 describes discrepancies in non-systematic AE data reported in conference abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD from RCTs testing gabapentin for neuropathic pain and quetiapine for bipolar depression. Our research broadens the existing evidence by comparing all available sources of data: conference abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD. We will also expand on the existing evidence by assessing whether non-systematic AE reporting is "complete" (i.e., data are reported in sufficient detail to be included in a meta-analysis) (70). If data about AEs differ across data sources, the information provided to healthcare stakeholders may be inaccurate.

Aim 2 compares the reporting of systematic AE data in conference abstracts, journal articles, clinical trial registries, CSRs, CSR-Synopses, and IPD from RCTs examining quetiapine for bipolar depression. Aim 2 adds to the current body of evidence because research about AE reporting has focused almost exclusively on non-systematic AE reporting. AEs are only collected systematically if there is reason to suspect that they might be related to the intervention (5); thus, systematic AEs are likely to be clinically important. The lack of research related to their reporting is a gap in the current evidence.

Aim 3 compares the consistency of "selection criteria" (i.e., the methods by which sources report that non-systematic AEs were selected for inclusion in the source) across trials and across sources about the same trial, as well as assessing the impact of using different selection criteria on meta-analyses. Aside from the ClinicalTrials.gov

reporting requirements (5), we were unable to identify any research related to assessing selection criteria for reporting non-systematic AEs. Aim 3 will attempt to fill this evidence gap.

Figure 1-1. Theoretical Framework: Data sources about randomized controlled trials and information gained from them



Chapter 2. Aim 1

Reporting of non-systematically collected adverse events in public and non-public sources about randomized clinical trials: Gabapentin for neuropathic pain and quetiapine for bipolar disorder as case examples

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Abstract

Background: Clinicians, guideline developers, and other healthcare stakeholders must have access to the evidence about both effectiveness and adverse events (AEs) of potential health interventions to make informed clinical decisions. AEs identified in randomized controlled trials (RCTs) are poorly reported, and reporting may differ by data source. The objective of this study was to compare reporting, in public and non-public sources, of non-systematic AEs (e.g., spontaneously reported by participants) observed in RCTs, including those designated by the Food and Drug Administration as "serious."

Methods and Findings: We performed a cross-sectional analysis using data from the Multiple Data Sources (MUDS) study, which examined sources of RCTs of gabapentin for neuropathic pain and quetiapine for bipolar depression ("eligible" RCTs). We identified public sources (i.e., journal articles, FDA reviews, trial registrations, conference abstracts and other short reports) and non-public sources (i.e., clinical study reports [CSRs], CSR-synopses, and individual participant data [IPD]) available by March 2, 2015 (gabapentin) and January 26, 2015 (quetiapine). We extracted data about non-systematic AEs, including those categorized as "serious" or not, as reported by trial investigators. We compared reporting of non-systematic AEs across public and non-public sources. We counted the number of different AEs and serious AEs that were reported by source; for example, a source reporting dizziness, confusion, and somnolence would be described

as reporting three different AEs. When AEs were reported in more than one source about the same trial, we compared the reported effect estimates.

We identified 21 eligible gabapentin trials (80 sources) and seven eligible quetiapine trials (52 sources). On average, public sources reported fewer different AEs than non-public sources (mean of 3 versus 121 and 3 versus 159 in public versus non-public sources, and for gabapentin and quetiapine, respectively). Most serious AEs were reported only in non-public sources (gabapentin: 56/72, 77%; quetiapine: 39/46, 85%). In rare cases when an AE was reported in multiple sources for the same trial, the effect estimates were similar.

Conclusions: Non-systematic AEs, including serious AEs, were often unreported in public sources. Better reporting and open access to non-public data are needed so that clinical decision-makers can assess the balance of potential benefits and AEs and base their healthcare decisions on the entire body of evidence.

Introduction

Patients, clinicians, and other decision makers need accurate and comprehensive information about potential benefits and adverse events (AEs) of healthcare interventions to inform decisions. AEs are defined by the Food and Drug Administration (FDA) as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (19). Health care decisions should be based on patient preferences and information about the balance of potential benefits and AEs for potential interventions.

Randomized controlled trials (RCTs) are the reference standard for determining the effectiveness and AEs of an intervention. During an RCT, information about AEs can be collected using two primary methods. The first method has been described as the "non-systematic" approach by the Final Rule, which outlines federal reporting requirements for ClinicalTrials.gov (Table 2-1) (5, 6). Non-systematic AEs may be collected as a result of spontaneous reports by participants to investigators or as a result of open-ended questions such as "have you noticed any symptoms since your last visit?" Investigators collect "systematic" AEs by recording, in the same manner for each trial participant, information about symptoms and events that are suspected of being associated with an intervention at the time the study is conducted (Table 2-1).

Although others distinguish between non-systematic and systematic AEs, some use different terminology. For example, the FDA uses "adverse events" to describe non-systematic AEs and "safety endpoints" or "safety assessments" to describe systematic

AEs (20). In terms of AEs, regulatory approval of drugs and biologics by the FDA requires collection of information about an intervention's effect on non-systematic AEs in RCTs, and is typically based on this information (4).

Both non-systematic and systematic AEs can be classified as "serious," an FDA classification that is standardized across trials. Serious AEs are defined by the FDA as "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (19, 20).

When patients are selecting a health intervention, they may be interested in the likely effectiveness as well as the different kinds of AEs and likelihood that they will experience the different AEs observed in trials. Yet, despite the importance of AEs to patients and clinicians, AEs are poorly reported in public sources across a variety of medical disciplines (28-34). Sources that are typically not publicly available (e.g., CSRs, individual participant data [IPD]) may contain more information about AEs than public sources (e.g., journal articles, conference abstracts) about the same trial (46, 48, 50, 69). For example, one case study showed that about 19% of AEs present in IPD were reported in journal articles (50). In addition, AE data may be publicly reported in some sources for a given trial but not in others (38, 39, 46, 48, 50, 69, 88, 89), or it can be inconsistently reported across sources for the same trial. Existing evidence typically has compared AE data in a few different sources, and we are unaware of studies that

compare all available source types for a single trial. Comparing all available sources enables the description of the relative completeness of each source type; for example, do trial registries contain more complete and accurate information about AEs than journal articles?

Our objectives in the current project were (1) to compare reporting of non-systematic AEs, with a focus on serious AEs, in a wide variety of public and non-public sources for two case studies and (2) to assess whether AE effect estimates vary among different sources. Our case studies were gabapentin for neuropathic pain and quetiapine for bipolar depression.

Methods

This analysis is a sub-study of the Multiple Data Sources (MUDS) study, a cross-sectional study that compares reporting of RCTs in public and non-public sources. The protocol (81) and protocol amendments (90) provide additional details about the MUDS study methods. We have also reported additional details in Appendix 2-1.

Eligible trials and sources

Briefly, eligible studies were parallel RCTs that compared either gabapentin for neuropathic pain in adults or quetiapine for bipolar depression in adults with placebo; participants and providers were masked. We use "public sources" to refer to journal articles, short reports (i.e., conference abstracts, commentaries, posters), trial registrations and associated results, and medical and statistical reviews created by the FDA. We use "non-public sources" to refer to clinical study reports (CSRs), CSR-synopses,

and IPD, because they are usually not available to the public. We searched for public and non-public sources and requested additional non-public sources from the company that manufactures quetiapine (see Appendix 2-1 and protocol (81) for additional details).

Data extraction

We classified AEs as systematic or non-systematic (5, 6). We pre-specified that we would classify AEs as systematic when they were reported as being obtained using specific measurement tools such as questionnaires, checklists, laboratory tests, and clinical examinations that were done on every patient. All other AEs were classified as non-systematic. Our analysis in this study focused exclusively on non-systematic AEs.

Two investigators independently extracted data about AEs using the open access Systematic Review Data Repository (SRDR; http://srdr.ahrq.gov/) and resolved any differences by discussion. We extracted the name of the non-systematic AE (e.g., dizziness, headache) and the associated results, such as the number or proportion of participants experiencing an AE, if available. We extracted results that were reported separately for each trial, and therefore did not extract data that were pooled from multiple trials. We extracted information about AEs even when results were not reported; for example, if a source reported that "the most common AEs were dizziness and headache," we extracted dizziness and headache as reported AEs. We extracted AE results closest to 8 and 18 weeks. We also extracted whether the source described the AE as serious (i.e., we did not classify AEs as serious if they were not reported that way).

Reanalysis of IPD

We did not receive meta-data (e.g., codebooks) for the IPD we obtained through litigation, making it difficult to interpret variables and the data contained in them. We used information in the corresponding CSRs (e.g., case report forms) to determine the meaning of the variables in the IPD. When databases were not available, we used ABBYY FineReader (91) to reconstruct databases using tables of IPD (in PDF format) in the appendices of CSRs. When both the IPD and CSR were available, we reanalyzed IPD data to assess agreement with what was reported in the associated CSR, replicating the methods for handling missing data used in the original trials. Using the IPD, we calculated the number of participants who experienced: (1) each named non-systematic AE, (2) each named *serious* non-systematic AE, (3) ≥1 non-systematic AE, and (4) ≥1 *serious* non-systematic AE. We performed all analyses using Stata 14 (92).

Comparing AEs across sources

To understand whether the reporting of non-systematic AEs was consistent across sources, we made the following comparisons: whether the non-systematic AE information was from a (1) public vs. non-public source, (2) journal article vs. non-public source, and (3) journal article vs. other public source. We compared the number of sources that reported non-systematic AEs and serious AEs. We also counted and compared the number of different non-systematic AEs and serious non-systematic AEs in each source. For example, if a source contained information about dizziness, confusion, and somnolence, the number of different AEs would be three. Across trials,

we compared the average number of different non-systematic AEs and serious non-systematic AEs reported in each source (e.g., the average number of different non-systematic AEs reported in journal articles across trials). For each individual trial, we compared the number of different non-systematic AEs and serious non-systematic AEs in public sources and non-public sources and used a Pearson's chi-squared test to examine statistical significance of our findings.

We anticipated that we would be able to obtain non-public sources for industry-funded trials only; CSRs and CSR-synopses are produced for industry trials, but not non-industry trials, and we did not request IPD separately from CSRs. To assess whether reporting of AEs was similar in trials with and without industry funding, we compared the mean number of different AEs reported in journal articles by industry funding and used a two-sided Student's t-test to examine statistical significance of our findings.

To assess whether different sources about the same trial reported the same results, we compared effect estimates (e.g., proportion of participants experiencing the AE) reported in different sources about the same trial. We created plots that showed all effect estimates for (1) experiencing any non-systematic AE(s) and (2) experiencing any serious non-systematic AE(s) in those taking gabapentin or quetiapine compared with placebo. For these plots, we combined the results from different doses of gabapentin or quetiapine from the same trial. For example, for a three-arm trial that compared 1800 milligrams (mg) gabapentin, 3600 mg gabapentin, and placebo, we combined the results of the two gabapentin arms for analysis.

For a trial's results to be considered "meta-analyzable" (90), the source had to report at least two of the following three pieces of information separately for each arm in the trial: number of participants experiencing the AE, percent of participants experiencing the AE, and number of participants analyzed. We considered information in IPD meta-analyzable. We assessed, for each different AE, how many trials reported meta-analyzable AE results and whether we could calculate the summary between groups effects (e.g., risk difference, relative risk) for each reported non-systematic AE. We compared summary data from all sources and summary data with non-public sources removed, to assess how excluding non-public sources would affect meta-analytic findings.

Results

Search results

We identified 80 sources (including six IPD) for 21 gabapentin trials and 52 sources (including two IPD) for 7 quetiapine trials (Appendix Figure 2-1). One gabapentin trial had no public source. Of the sources we identified, most were public: 68/80 (85%) for gabapentin and 46/52 (88%) for quetiapine. Most public sources were short reports (gabapentin: 35/68, 51%; quetiapine: 24/46, 52%), followed by journal articles (gabapentin: 26/68, 38%; quetiapine: 15/46, 33%). The majority of trials we identified were completed or published by 2005: 14/21 (67%) gabapentin trials and 4/7 (57%) quetiapine trials.

We requested CSRs and IPD from Pfizer, the company that bought the companies that originally supported nine gabapentin trials, but had not received any data from them by October 16, 2017. Although we requested additional CSRs and IPD from Astra Zeneca, the company performing all seven quetiapine trials, our request was denied (93).

We used CSRs and IPD available from unsealed litigation for 6/9 gabapentin trials; the IPD were electronic and in database format. We obtained CSRs for two trials and CSR-synopses for two quetiapine trials by searching online (http://psychrights.org/).The first CSR included extensive IPD tables. Based on other information in the second CSR, we know that the IPD tables in the second CSR did not contain data about all the non-systematic AEs that occurred in the trial. Rather, the IPD tables containing non-systematic AEs included serious AEs, AEs leading to withdrawal from the study, and AEs "of interest."

Comparing reanalyzed IPD with CSRs

We identified discrepancies between CSRs and IPD for the same trial. For 5/6 gabapentin trials and both quetiapine trials, we identified more different AEs in the CSR than in the IPD; in addition, there were many AEs in the IPD that we were unable to identify. For one gabapentin trial (A945-1008), there appeared to be many discrepancies between the CSR and IPD. The CSR for this trial reported that the summary data in the CSR and the IPD were coded for analysis using different methods, so it is expected that the names of the AEs do not agree.

Public sources underreported non-systematic adverse events

On average, public sources described fewer different AEs than non-public sources (gabapentin: mean of 3 vs. 121 different AEs; quetiapine: mean of 3 vs. 159 different AEs). Across all eligible trials, a total of 341/419 (81%) and 436/471 (93%) different AEs were reported only in non-public sources for gabapentin and quetiapine, respectively (Appendix Table 2-1). Similarly, the majority of different serious AEs were reported only in non-public sources: 56/72 (78%) in gabapentin trials and 39/46 (85%) in quetiapine trials.

The mean number of different AEs reported varied by source, even when the sources compared were all public or all non-public. Journal articles described a mean of 5 and 7 different AEs, while other public sources, such as ClinicalTrials.gov, reported a mean of 3 and 2 different AEs, for gabapentin and quetiapine respectively. FDA reviews reported AE data pooled from multiple trials so we could not analyze the information. CSR-synopses reported a mean of 19 different AEs, while CSRs reported a mean of 123 and 297 different AEs for gabapentin and quetiapine, respectively.

For both gabapentin and quetiapine, public sources frequently omitted data about non-systematic AEs that were almost always present in non-public sources (Figure 2-1, Table 2-2). For example, 8/68 (12%) public gabapentin sources and 4/46 (9%) public quetiapine sources reported the number of participants who experienced any AE, compared with 12/12 (100%) and 6/6 (100%) non-public sources and the number of participants who experienced any serious AE were often not reported in public sources

(Figure 2-1, Table 2-2). Journal articles reported data about non-systematic AEs more often than other public sources, but still less often than non-public sources (Table 2-3).

When we compared public with non-public sources about the same trial (6 trials for gabapentin and 4 trials for quetiapine had both types of sources), we found that public sources contained data about significantly fewer non-systematic AEs (Pearson's chi square, $p<0.001$ for both gabapentin and quetiapine). Whereas public sources typically reported few different AEs, non-public sources reported hundreds of different AEs about the same trial (Figure 2-2). We also found that public sources reported fewer different serious AEs compared to non-public sources (Pearson's chi square, $p<0.001$ for both gabapentin and quetiapine). Whereas public sources reported serious AEs for 2/10 trials, 10/10 non-public sources reported serious AEs.

Because CSRs (non-public) are produced only for industry trials, we could not compare the number of different AEs reported in public sources with non-public sources for trials without industry funding. When we compared the number of different AEs reported in journal articles about 27 (20 gabapentin and 7 quetiapine) trials with and without industry funding, we found no evidence of a difference. Journal articles about trials with industry funding reported an average of 6 (standard deviation=6) different non-systematic AEs, while journal articles about trials without industry funding reported an average of 3 (standard deviation=2) different non-systematic AEs ($p=0.193$).

Meta-analyses of adverse event data from public sources would include few trials

When effect estimates for non-systematic AEs for one trial appeared in multiple sources, the estimates were similar or identical to one another (Figure 2-3). We were rarely able to compare the estimates in public and non-public sources; public sources often did not report the data, and non-public sources were often unavailable.

Even when meta-analyzable data on non-systematic AEs were available, they were not usually available in a public source (Appendix Table 2-1). Meta-analyzable results were reported only in non-public sources for 349/411 (85%) and 439/462 (95%) different non-systematic AEs for gabapentin and quetiapine, respectively (Appendix Table 2-1). Similarly, meta-analyzable results were reported only in non-public sources for 54/70 (77%) and 37/38 (97%) different serious AEs.

Without non-public sources such as CSRs and IPD, meta-analyses of AE data were largely impossible or could include few trials (Appendix Tables 2-2 and 2-3). For example, if a meta-analysis were conducted of the risk of experiencing any non-systematic AE comparing gabapentin or quetiapine with placebo, 9/21 and 6/7 trials could be included. When we limited the meta-analyses to data from public sources, the meta-analyses included 5/21 gabapentin trials and 3/7 quetiapine trials. We found similar results when examining the number of participants who experienced any serious AE(s), as well as specific AEs and specific serious AEs (Appendix Tables 2-2 and 2-3).

Discussion

Compared with non-public sources, public sources reported fewer different non-systematic AEs occurring in gabapentin and quetiapine trials. The majority of AEs were reported only in non-public sources. Almost all AE data in non-public sources were meta-analyzable, while few AEs reported in public sources were. We have demonstrated that, for these two interventions, using public sources alone would result in healthcare stakeholders lacking information about most non-systematic AEs.

Similarly, most serious AEs were not described at all in public sources, implying that most patients and their doctors would not have this knowledge. When serious AEs were reported in public sources, they were often not meta-analyzable, meaning that researchers would not be able to assess the likelihood that patients would experience each different serious AE. Journal articles, which typically serve as the main source of data for clinical decision-makers, reported little or no data about serious AEs. When serious AEs are unreported in public sources, clinical decision-makers lack information critical to selecting an intervention.

Public sources frequently did not report the number of participants who described having any non-systematic AE or any non-systematic serious AE. When AE data were reported in both public and non-public sources about the same trial, the effect estimates were similar. We frequently could not compare public and non-public sources, however, because of serious under-reporting in the public sources and inaccessibility of non-public sources.

Although we examined only two interventions and indications in our analysis, we believe our findings may apply to other interventions. Our findings were similar for both interventions, despite the differences in indication, drug class, and time-period of the eligible trials. In addition, our findings are consistent with previous studies that compared public and non-public sources (46, 48, 50, 69). In contrast, our results differ from studies that showed ClinicalTrials.gov to be more complete than journal articles (38, 39, 89); we found ClinicalTrials.gov may not be a good source of information about AEs when the trials were conducted before registration was required by funders and journal editors (79).

CSR-synopses do not contain much more information than public sources and should not be considered an acceptable substitute for CSRs or IPD for examining non-systematic AEs. CSRs reported meta-analyzable data where CSR-synopses did not, and CSRs and IPD both reported many more non-systematic AEs and serious AEs than CSR-synopses. FDA reviews were also not a good source of data about non-systematic AEs; while they did contain data about AEs, the data were pooled across trials, rather than reported separately for each trial.

A limitation of our study is that we identified non-public sources only for industry-funded trials, so we could not compare public with non-public sources for trials with other funding. Reporting of non-systematic AEs was similar in journal articles about RCTs with and without industry funding, however. Therefore, underreporting of AEs may be as big a problem in non-industry trials as it is appears to be in industry trials.

Because CSRs are available only for industry trials, IPD may provide the additional information about AEs in non-industry trials needed to make informed healthcare decisions, as long as the meta-data (e.g., codebooks) for the IPD are provided.

It is important for patients to be able to use information about benefits and AEs to inform their healthcare decisions, for example, using "scenario planning" (94). This involves the doctor discussing best, worst, and mostly likely scenarios following treatment. For example, the "worst" scenario for gabapentin or quetiapine might be that the treatment doesn't show any benefit and also causes some harm AEs. The "best" scenario might be that the patient's symptoms are completely alleviated and they experience no AEs. The most likely scenario may involve some benefit and some harm. The doctor and patient can discuss what the likely AEs are and whether these may outweigh the likely benefits, as well as how scenarios may differ across treatment options. Doctors must have comprehensive information about both benefits and harms in order to construct the different scenarios. When harms are not reported in public sources, doctors may be unable to describe the likelihood of the worst scenario or compare scenarios for different treatment options.

"Open science" and data sharing present a possible way to address poor reporting of AEs. Data can be shared in many ways: on clinical trial registries (e.g., ClinicalTrials.gov); directly with other investigators who request data (e.g., systematic reviewers who contact authors of journal articles to request data); on a public portal (e.g., ClinicalStudyDataRequest.com (78)); or on a private server or website. Although

many commonly prescribed medications currently in use were approved many years ago, many data sharing policies exclude older trials, so obtaining relevant data can be difficult. For example, ClinicalTrials.gov only requires the registration of trials completed after 2007 (80). The International Committee of Medical Journal Editors (ICMJE) required trial registration for publication starting in 2005 (79). Data sharing on public portals may also be limited to trials completed after a certain date. On ClinicalStudyDataRequest.com, for example, data-sharing policies vary by trial sponsor, but most date requirements are 2010 or later (78).

Our findings demonstrate the need for open science and data sharing to combat the poor reporting of AEs, not only for new trials, but older trials about medications that are widely used in medical practice (95). Currently, non-public sources, especially for older trials, can be difficult to obtain. Non-public sources can also be difficult to use. While it took only a few hours to extract data from each journal article, it took weeks to extract all trial data from the CSRs we obtained, which were an average of 2900 pages long. In addition, since we did not receive meta-data (e.g., codebooks) for IPD, we spent months deciphering the meaning of the variables in the databases we received. Even with extensive work, there were some variables that we could not identify. In our analysis, where it was not necessary to perform additional analyses using IPD (e.g., subgroup analyses not performed during the original trial analysis), the aggregate data provided in CSRs were much easier to use and provided just as much or more information than the IPD. While it can be time- and resource-intensive to extract data

from CSRs or analyze IPD without appropriate meta-data, CSRs and IPD provide a much more complete picture of the potential harms of a medication than journal articles or CSR-synopses. With access to currently non-public sources, all healthcare stakeholders would be able to incorporate all available evidence in their decision-making.

Table 2-1. Glossary of Terms

Term	Definition
Adverse events	
Non-systematic adverse events (Final Rule)	Adverse events that are collected using open-ended questions or are spontaneously reported by participants. For example, adverse events collected by asking participants questions like "Have you noticed any symptoms since your last examination?"
Systematic adverse events (Final Rule)	Adverse events that are collected in the same manner for each participant using methods related to specific adverse events. For example, adverse events collected using validated questionnaires, checklists, laboratory measurements, or vital signs.
Serious adverse events	AEs classified according to definitions determined by regulatory agencies. The Food and Drug Administration and European Medicines Agency define serious AEs as "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (19).
Sources	
Public sources	In this study, public sources include journal articles, conference abstracts, commentaries, posters, trial registrations and associated results, and medical and statistical reviews created by the Food and Drug Administration.
Non-public sources	In this study, non-public sources include individual patient data, clinical study reports, and clinical study report-synopses.
Clinical study report (CSR)	A comprehensive document created by a pharmaceutical company detailing the design, methods, analyses, and results of a single study for submission to regulatory agencies. The clinical study reports we examined ranged in length from 1315 to 8027 pages. Appendices contain tables of individual participant data, also called "patient data listings."
Clinical study report synopsis (CSR-synopsis)	An internal company document that summarizes the information contained in clinical study reports. Clinical study report-synopses are much shorter than clinical study reports; the two clinical study report-synopses we examined were each 13 pages in length.
Individual participant data (IPD)	Each record lists data separately for each participant. In the below example, the data include a participant identifier ("PTNO"), text describing the adverse event ("AETX"), whether the AE was classified as serious ("AESER"), the day of the study that the event occurred ("SDAESTDY"), and a standardized code for grouping AEs that are clinically equivalent ("AE"; e.g., "giddy" and "giddiness" have the same code). There is a separate record for each participant and each different AE. For example, participant 167 experienced three different AEs (tiredness, headache, and septic foot).

PTNO	AETX	AESER	SDAESTDY	
163	DROWSINESS	0	2	079
164	GIDDY	0	28	075
166	GIDDINESS	0	2	075
167	TIREDNESS	0	11	001
167	HEADACHE	0	16	010
167	SEPTIC FOOT	0	22	008

Table 2-2. Number of public and non-public sources with information about non-systematic adverse events

Table 2-2 Legend: Each source is counted only once, regardless of whether the source describes one adverse event or more than one adverse event). Public sources include journal articles, conference abstracts, FDA reviews, trial registrations, and other short reports (i.e., letters to the editor, posters, press releases, reports in trade publications). Non-public sources include clinical study reports (CSRs), CSR-synopses, and individual participant data (IPD).

AE = adverse event; **N** = total number of sources (e.g., there are 68 public sources for gabapentin); **n** = number of sources describing each characteristic by category (e.g., 8/68 public sources for gabapentin described participants who experienced any adverse event; 7/68 public sources described participants who experienced any adverse event in enough detail to be included in a meta-analysis); **%** = percentage.

	Gabapentin for neuropathic pain				**Quetiapine for bipolar depression**			
	Public Sources N=68		**Non-Public Sources N=12**		**Public Sources N=46**		**Non-Public Sources N=6**	
Number of sources including AE data	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants experiencing ≥1 AE	8	(12%)	12	(100%)	4	(9%)	6	(100%)
Specific adverse events	31	(46%)	12	(100%)	22	(48%)	6	(100%)
Participants experiencing ≥1 serious AE	9	(13%)	12	(100%)	6	(13%)	6	(100%)
Specific serious adverse events	4	(6%)	12	(100%)	1	(2%)	6	(100%)
Number of sources including meta-analyzable AE data								
Participants experiencing ≥1 AE	7	(10%)	12	(100%)	3	(7%)	6	(100%)
Specific adverse events	18	(26%)	12	(100%)	7	(15%)	6	(100%)
Participants experiencing ≥1 serious AE	4	(6%)	12	(100%)	4	(9%)	6	(100%)
Specific serious adverse events	3	(4%)	12	(100%)	1	(2%)	6	(100%)

Table 2-3. Number of journal articles and other public sources with information about non-systematic adverse events

Table 2-3 Legend: Each source is counted only once, regardless of whether the source describes one adverse event or more than one adverse event). Other public sources include conference abstracts, FDA reviews, trial registrations, and other short reports (i.e., letters to the editor, posters, press releases, reports in trade publications).

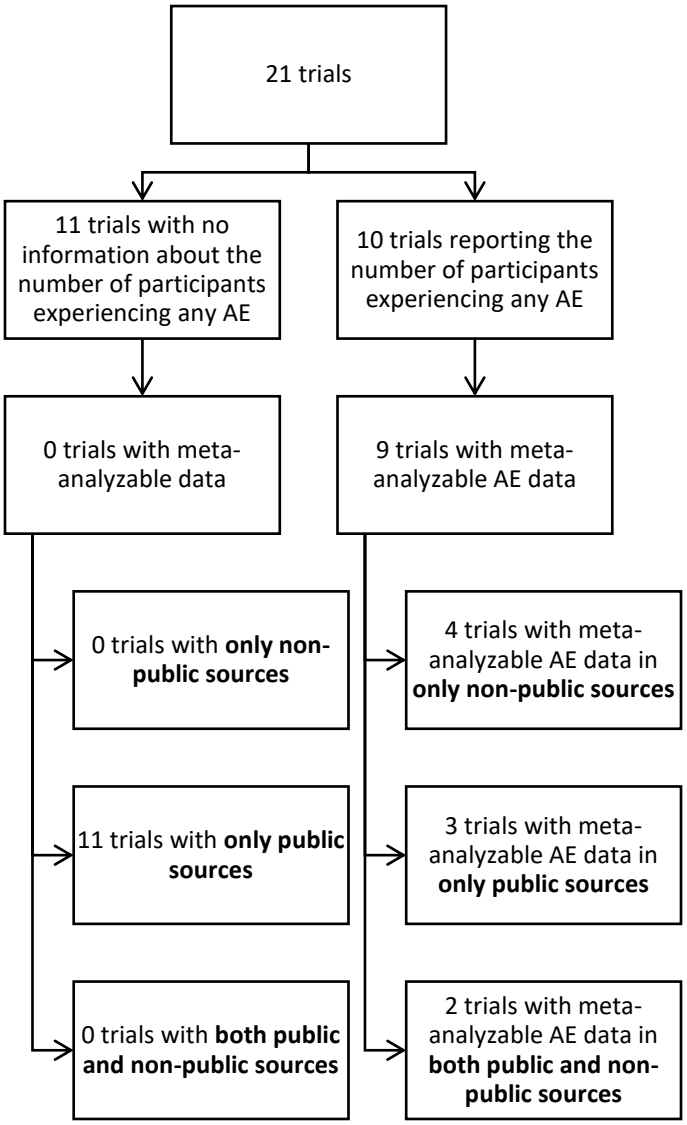
AE = adverse event; **N** = total number of sources (e.g., there are 26 journal articles for gabapentin); **n** = number of sources describing each characteristic by category (e.g., 7/26 journal articles for gabapentin described participants who experienced any adverse event; **%** = percentage.

	Gabapentin for neuropathic pain				**Quetiapine for bipolar depression**			
	Journal Articles N=26		**Other Public Sources N=42**		**Journal Articles N=15**		**Other Public Sources N=31**	
Number of sources including AE data	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants experiencing ≥1 AE	7	(27%)	1	(2%)	2	(13%)	2	(6%)
Specific adverse events	18	(69%)	13	(31%)	11	(73%)	11	(35%)
Participants experiencing ≥1 serious AE	6	(23%)	3	(7%)	5	(33%)	1	(3%)
Specific serious adverse events	3	(12%)	1	(2%)	1	(7%)	0	(0%)
Number of sources including meta-analyzable AE data								
Participants experiencing ≥1 AE	6	(23%)	1	(2%)	2	(13%)	1	(3%)
Specific adverse events	14	(54%)	4	(10%)	6	(40%)	1	(3%)
Participants experiencing ≥1 serious AE	2	(8%)	2	(5%)	3	(20%)	1	(3%)
Specific serious adverse events	2	(8%)	1	(2%)	1	(7%)	0	(0%)

Figure 2-1. Number of trials reporting or recording participants experiencing any non-systematic adverse event

Figure 2-1 Legend: Data were considered "meta-analyzable" when a between group effect could be calculated (e.g., both the number of participants experiencing an adverse event and the number of participants analyzed were reported).

2-1a. Gabapentin for neuropathic pain



2-1b. Quetiapine for bipolar depression

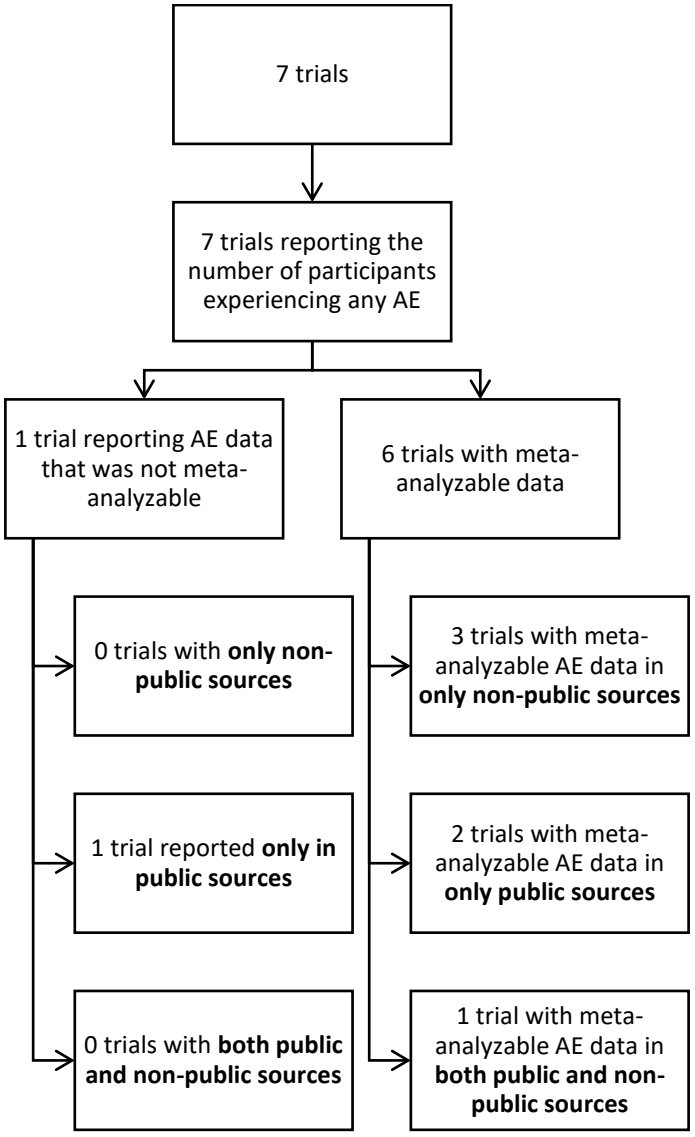
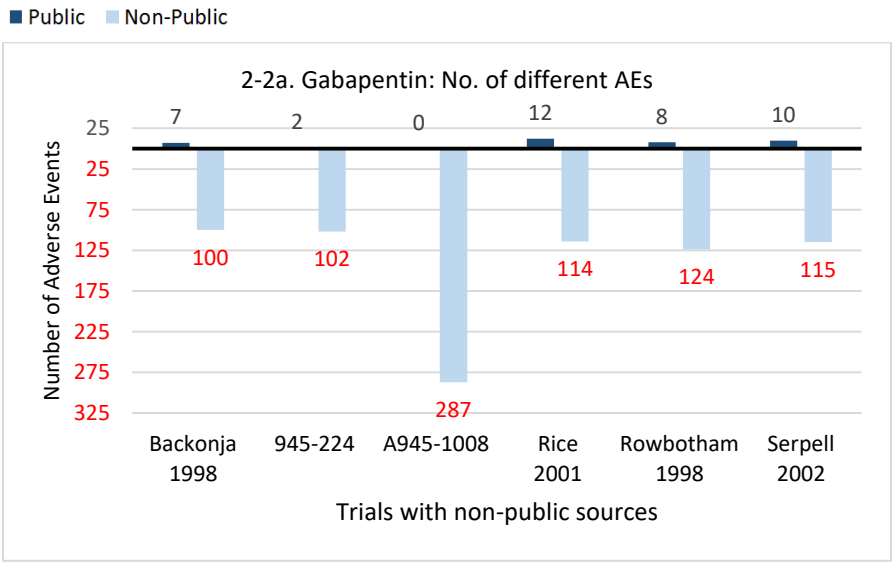


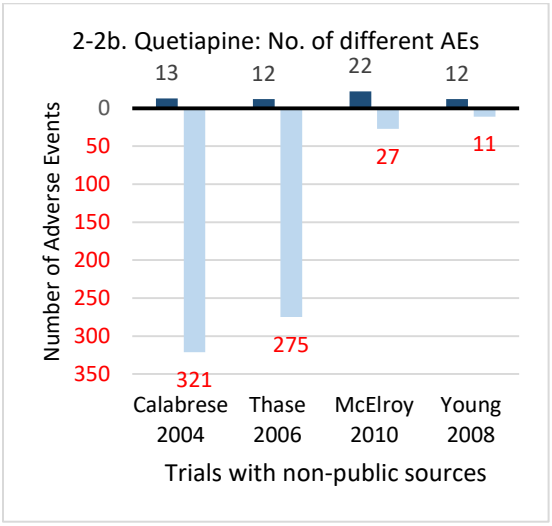
Figure 2-2. Number of different non-systematic adverse events reported in public and non-public sources by trial

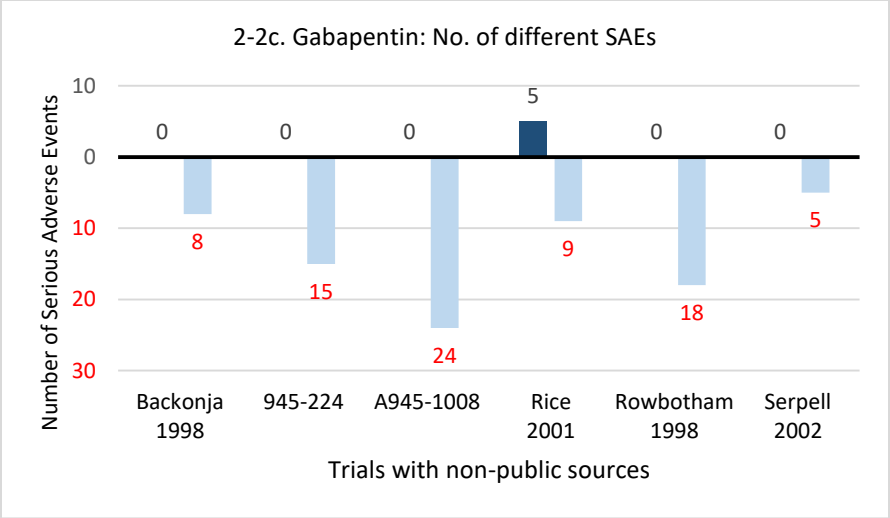
Figure 2-2 Legend: **Note:** the axes are different for each panel to make the figure easier to read and numbers of different AEs for each source provided by trial. Public sources include journal articles, conference abstracts, Food and Drug Administration reviews, trial registrations, and other short reports. Non-public sources include clinical study reports (CSRs), CSR-synopses, and individual participant data (IPD). This figure includes CSRs and IPD for all gabapentin trials and Calabrese 2004 and Thase 2006 (quetiapine trials). This figure includes only CSR-synopses for McElroy 2010 and Young 2008.

No. of different AEs: Number of different specific AEs reported in each source. For example, if a source contained data about dizziness, confusion, and somnolence, the number of different adverse events would be 3. This includes adverse events that are described without numerical data (i.e., ranged from a mention to data that were not meta-analyzable to meta-analyzable data).

No. of different SAEs: Number of different specific serious AEs reported in each source (counted as described above).






2-2c. Gabapentin: No. of different SAEs
Number of Serious Adverse Events
10
0
10
20
30
0
0
0
5
0
0
8
15
24
9
18
5
Backonja 1998
945-224
A945-1008
Rice 2001
Rowbotham 1998
Serpell 2002
Trials with non-public sources

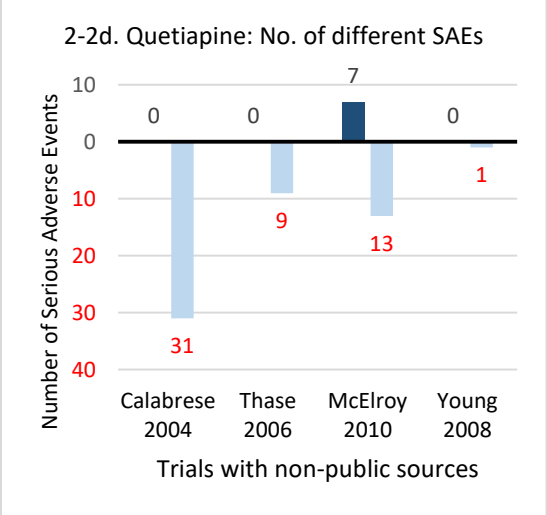
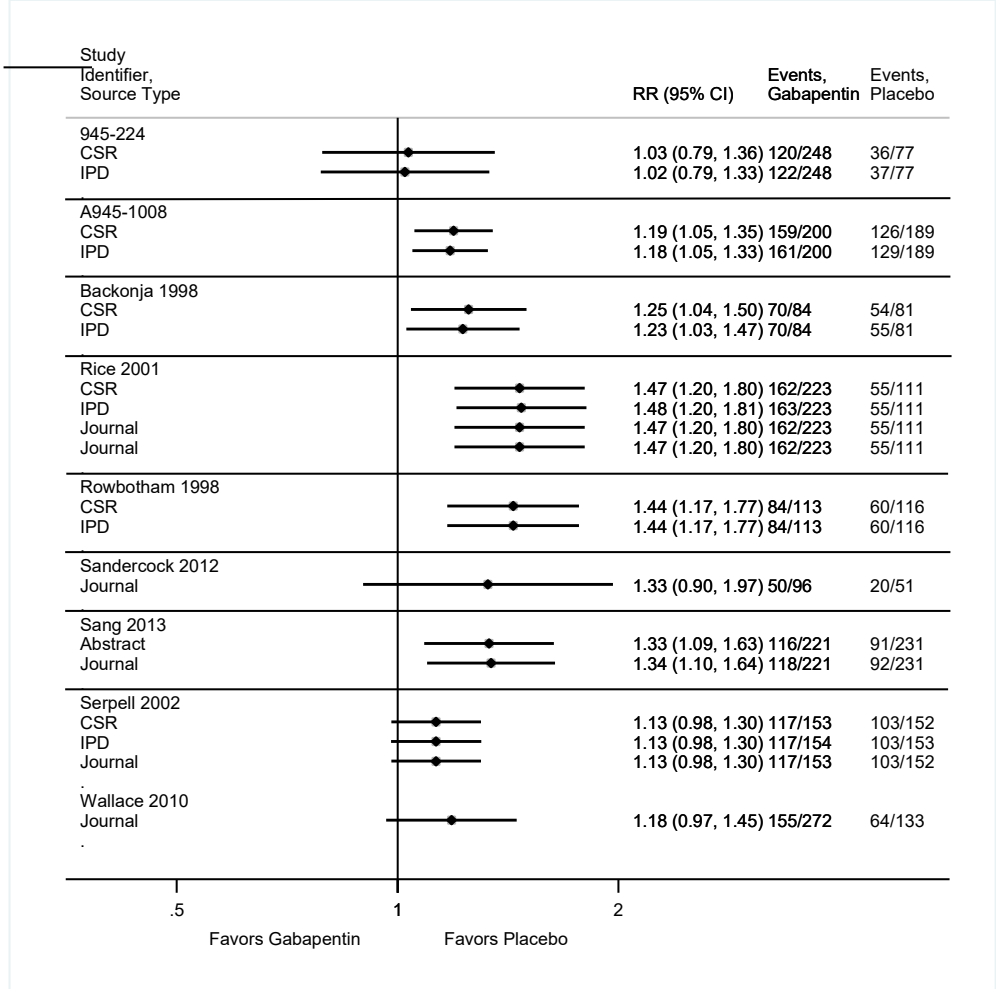

2-2d. Quetiapine: No. of different SAEs
Number of Serious Adverse Events
10
0
10
20
30
40
0
0
7
0
31
9
13
1
Calabrese 2004
Thase 2006
McElroy 2010
Young 2008
Trials with non-public sources

Figure 2-3. Relative risk (95% confidence interval) of experiencing any non-systematic adverse event comparing gabapentin or quetiapine with placebo, by trial and source

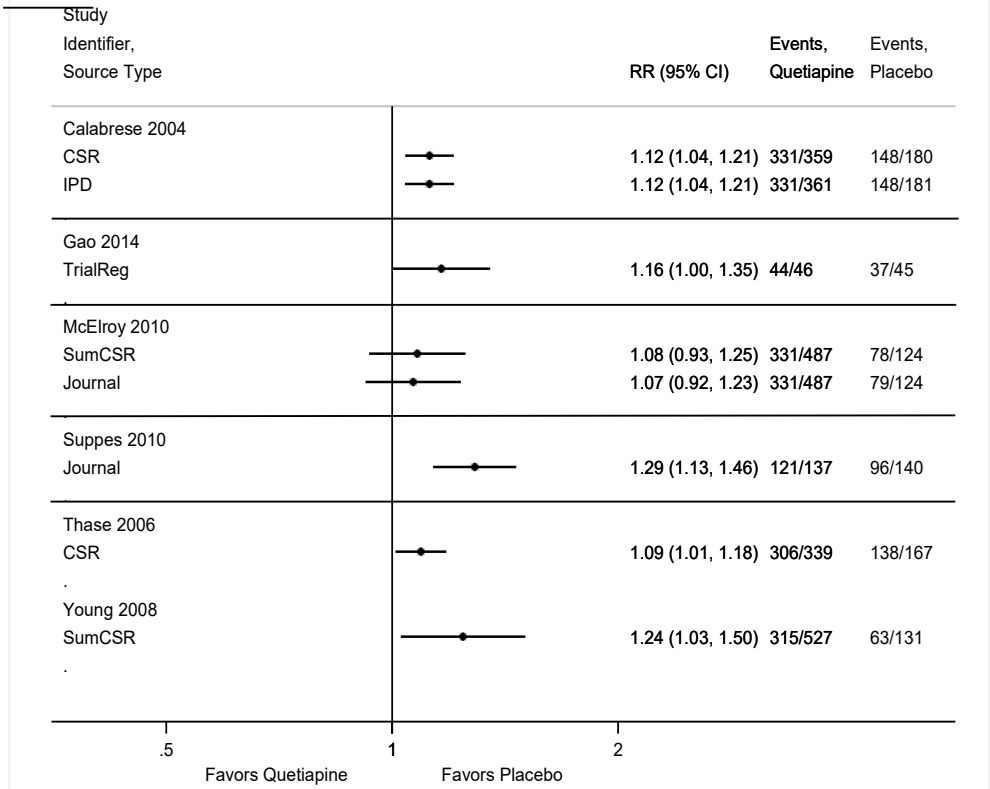
Figure 2-3 Legend: Public sources include journal articles, conference abstracts, FDA reviews, trial registrations, and other reports (i.e., letters to the editor, posters, press releases, reports in trade publications). Non-public sources include clinical study reports (CSRs), CSR-synopses, and individual participant data (IPD). **Panel 2-3a** shows only the 9/21 gabapentin trials for which we could calculate the relative risk from data in at least one source. The remaining 12/21 gabapentin trials did not report meta-analyzable data for the number of participants experiencing any adverse event in any data source. We did not have non-public sources for any of these 12 trials. **Panel 2-3b** shows only the 6/7 trials for which we could calculate the relative risk from data in at least one source. The remaining trial did not report meta-analyzable data for the number of participants experiencing any adverse event in any data source. We did not have non-public sources for this trial. Not all trials have data from all sources; for example, we could only calculate the relative risk and 95% confidence interval for Backonja 1998 using the CSR and IPD.

CSR = clinical study report; **IPD** = individual participant data; **RR** = relative risk; **CI** = confidence interval

Panel 2-3a: Gabapentin for neuropathic pain



Panel 2-3b: Quetiapine for bipolar depression



Appendix 2-1. Detailed methods

Identifying sources about eligible trials

We searched both the International Clinical Trials Registry Platform Search Portal (ICTRP) and ClinicalTrials.gov for trial registrations and associated results related to gabapentin or quetiapine on October 10, 2014. We searched PubMed, Embase, Lilacs, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) for gabapentin and quetiapine sources, as well as PsycInfo for quetiapine; we completed our searches March 2, 2015 (gabapentin) and January 26, 2015 (quetiapine), without any language restrictions. We identified medical and statistical reviews of gabapentin as well as quetiapine available on the FDA website (31). We also searched certain conference proceedings and years for gabapentin trials (see protocol (1)). We searched online (http://psychrights.org/) for typically non-public sources about quetiapine for bipolar depression. We requested non-public sources in the form of internal company documents from the manufacturers of gabapentin and quetiapine (Pfizer and AstraZeneca, respectively). We identified the trial(s) reported in each source and grouped sources by the trial(s) described.

Appendix Table 2-1. Number of different adverse events reported by trial and source

Appendix Table 2-1 Legend: This table shows, by trial and source, the number of different adverse events and the number of different adverse events that were reported in enough detail to be included in a meta-analysis.

[1] CSR-synopses (CSR-S) were available only for quetiapine. FDA reviews were available only for gabapentin.

1 trial = journal article about a single eligible trial; ≥**2 trials** = journal article about two or more eligible trials; **Abstract** = conference abstract; **Registration=** trial registration on ClinicalTrials.gov or another registry; **FDA** = Food and Drug Administration medical or statistical review; **Other** = letters, summaries of journal articles, press releases, brief reports in trade publications (e.g., not peer reviewed); **CSR-S** = clinical study report-synopsis; **CSR** = clinical study report; **IPD** = individual participant data; **N/A =** not applicable because there are no reports.

Different adverse events: Number of different specific adverse events reported in each source. For example, if a source contained data about dizziness, confusion, and somnolence, the number of different adverse events would be three. This includes adverse events that are described without numerical data (e.g., the most common adverse events were headache and nausea). **Different adverse events with meta-analyzable data:** Number of different adverse events for which the between group effect size could be calculated (e.g., source reported number of participants with the AE and the total number analyzed).

	Public Sources							Non-Public Sources				
	Journal Articles		Short Reports									
Trial Identifier	1 Trial	>1 Trial	Abstract	Other	Registration	FDA [1]	All Public	CSR-S[1]	CSR	IPD	All Non-Public	All Sources
Different adverse events (Different adverse events with meta-analyzable data)												
Gabapentin for neuropathic pain												
945-224 (96-101)	N/A	2 (0)	0 (0)	0 (0)	N/A	N/A	2 (0)	N/A	97 (97)	86 (86)	102 (102)	102 (102)
A945-1008 (102)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	199 (199)	210 (210)	287 (287)	287 (287)
Arai 2010 (103, 104)	3 (3)	N/A	1 (0)	N/A	N/A	N/A	4 (3)	N/A	N/A	N/A	N/A	4 (3)
Backonja 1998 (96-100, 105-113)	7 (6)	2 (0)	3 (0)	3 (0)	N/A	N/A	7 (6)	N/A	97 (97)	91 (91)	100 (100)	101 (100)
Caraceni 2004 (114-116)	26 (25)	N/A	N/A	24 (24)	N/A	N/A	26 (26)	N/A	N/A	N/A	N/A	26 (26)
Hahn 2004 (117)	5 (5)	N/A	N/A	N/A	N/A	N/A	5 (5)	N/A	N/A	N/A	N/A	5 (5)
Hui 2010 (118, 119)	7 (0)	N/A	N/A	N/A	0 (0)	N/A	7 (0)	N/A	N/A	N/A	N/A	7 (0)
Irving 2009 (120, 121)	12 (9)	N/A	N/A	N/A	N/A	N/A	12 (9)	N/A	N/A	N/A	N/A	12 (9)
Milenkovic 2009 (122)	N/A	N/A	0 (0)	N/A	N/A	N/A	0 (0)	N/A	N/A	N/A	N/A	0 (0)
Mishra 2012 (123)	0 (0)	N/A	N/A	N/A	N/A	N/A	0 (0)	N/A	N/A	N/A	N/A	0 (0)
NCT00475904 (124)	N/A	N/A	N/A	N/A	1 (1)	N/A	1 (1)	N/A	N/A	N/A	N/A	1 (1)
Rice 2001 (96-100, 125-132)	12 (12)	3 (0)	0 (0)	0 (0)	N/A	1 (0)	12 (12)	N/A	113 (109)	104 (104)	114 (110)	114 (111)
Rowbotham 1998 (96-100, 125-128, 133-136)	8 (8)	5 (0)	0 (0)	5 (0)	N/A	1 (0)	8 (8)	N/A	122 (122)	120 (120)	124 (124)	125 (125)

Sandercock 2012 (137-139)	6 (1)	N/A	N/A	2 (0)	0 (0)	N/A	6 (1)	N/A	N/A	N/A	N/A	6 (1)
Sang 2013 (140-156)	6 (6)	0 (0)	2 (2)	0 (0)	26 (26)	N/A	26 (26)	N/A	N/A	N/A	N/A	26 (26)
Serpell 2002 (96-100, 128, 157-160)	10 (10)	2 (0)	0 (0)	0 (0)	N/A	N/A	10 (10)	N/A	114 (111)	103 (103)	115 (112)	115 (112)
Simpson 2001 (161, 162)	6 (6)	N/A	0 (0)	N/A	N/A	N/A	6 (6)	N/A	N/A	N/A	N/A	6 (6)
Tamez Pérez 2000 (163, 164)	0 (0)	N/A	N/A	1 (0)	N/A	N/A	1 (0)	N/A	N/A	N/A	N/A	1 (0)
Wallace 2010 (140-152, 165-167)	6 (6)	0 (0)	0 (0)	N/A	0 (0)	N/A	6 (6)	N/A	N/A	N/A	N/A	6 (6)
Yildirim 2003 (168)	2 (0)	N/A	N/A	N/A	N/A	N/A	2 (0)	N/A	N/A	N/A	N/A	2 (0)
Zepeda Vazquez 2001 (169)	4 (4)	N/A	N/A	N/A	N/A	N/A	4 (4)	N/A	N/A	N/A	N/A	4 (4)
Total	**51 (47)**	**5 (0)**	**4 (2)**	**28 (24)**	**26 (26)**	**1 (0)**	**68 (62)**	**N/A**	**304 (297)**	**329 (329)**	**391 (384)**	**419 (411)**
Quetiapine for bipolar depression												
Calabrese 2004 (170-195)	13 (10)	1 (0)	5 (0)	0 (0)	0 (0)	N/A	13 (10)	N/A	319 (319)	316 (316)	321 (321)	324 (322)
Gao 2014 (196, 197)	9 (9)	N/A	N/A	N/A	8 (8)	N/A	9 (9)	N/A	N/A	N/A	N/A	9 (9)
Li 2014 (198, 199)	N/A	N/A	N/A	N/A	0 (0)	N/A	5 (0)	N/A	N/A	N/A	N/A	5 (0)
McElroy 2010 (170-176, 200-204)	22 (15)	0 (0)	7 (0)	0 (0)	0 (0)	N/A	22 (15)	27 (15)	N/A	N/A	27 (15)	29 (16)
Suppes 2010 (205-207)	15 (14)	N/A	3 (0)	N/A	0 (0)	N/A	15 (14)	N/A	N/A	N/A	N/A	15 (14)
Thase 2006 (170-180, 208-213)	11 (8)	1 (0)	0 (0)	2 (0)	0 (0)	N/A	12 (8)	N/A	275 (275)	9 (9)	275 (275)	279 (275)
Young 2008 (170-176, 200, 214-219)	11 (10)	0 (0)	4 (0)	1 (0)	0 (0)	N/A	12 (10)	11 (11)	N/A	N/A	11 (11)	13 (11)
Total	**33 (23)**	**1 (0)**	**9 (0)**	**3 (0)**	**8 (8)**	**N/A**	**35 (23)**	**28 (16)**	**456 (456)**	**320 (320)**	**463 (459)**	**471 (462)**

Appendix Table 2-2. Gabapentin trials with data that could be included in a meta-analysis, by whether the data source is public

Appendix Table 2-2 Legend: For example, when including data from any source, 6/21 (29%) trials reported meta-analyzable results for the number of participants who experienced abdominal pain. When including only data from public sources, 1/21 (5%) trials reported meta-analyzable results for the number of participants who experienced abdominal pain.

The first section of the table includes the number of participants experiencing any AE(s) and the number of participants experiencing any serious AE(s).

The second section of the table includes specific adverse events (in alphabetical order) for which meta-analyzable data were reported in a public source for at least one trial, followed by specific adverse events (in alphabetical order) for which meta-analyzable data were not reported in any public sources.

The third section of the table includes specific serious adverse events (in alphabetical order) for which meta-analyzable data were reported in a public source for at least one trial, followed by specific serious adverse events (in alphabetical order) for which meta-analyzable data were not reported in any public sources.

	Gabapentin for neuropathic pain (N=21 trials)	
	Trials with meta-analyzable data across all sources No. (%)	**Trials with meta-analyzable data across public sources No. (%)**
Aggregated adverse events		
No. participants experiencing ≥1 AE	9 (43%)	5 (24%)
No. participants experiencing ≥1 serious AE	9 (43%)	4 (19%)
Named adverse events		
Abdominal Pain	6 (29%)	1 (5%)
Accidental Injury	6 (29%)	1 (5%)
Asthenia	6 (29%)	1 (5%)
Ataxia	6 (29%)	1 (5%)
Confusion	7 (33%)	2 (10%)
Constipation	7 (33%)	1 (5%)
Death	4 (19%)	3 (14%)
Diarrhea	7 (33%)	4 (19%)
Dizziness	11 (52%)	9 (43%)
Dry Mouth	8 (38%)	3 (14%)
Edema Peripheral	9 (43%)	5 (24%)
Fatigue	2 (10%)	1 (5%)
Flu Syndrome	6 (29%)	1 (5%)
Gait Ataxia	1 (5%)	1 (5%)
Gait Disturbance	1 (5%)	1 (5%)
Headache	12 (57%)	8 (38%)
Infection	6 (29%)	2 (10%)
Nasopharyngitis	1 (5%)	1 (5%)
Nausea	12 (57%)	8 (38%)
Pain	6 (29%)	1 (5%)
Sedation	1 (5%)	1 (5%)
Somnolence	11 (52%)	9 (43%)

Upper Respiratory Tract Infection	2 (10%)	1 (5%)
Vertigo	5 (24%)	1 (5%)
Abnormal Dreams	4 (19%)	0 (0%)
Abnormal Gait	3 (14%)	0 (0%)
Abnormal Stools	2 (10%)	0 (0%)
Abnormal Vision	4 (19%)	0 (0%)
Abscess	2 (10%)	0 (0%)
Accidental Fall	1 (5%)	0 (0%)
Acne	3 (14%)	0 (0%)
Agitation	2 (10%)	0 (0%)
Akinesia	1 (5%)	0 (0%)
Albuminuria	1 (5%)	0 (0%)
Alkaline Phosphatase Increased	1 (5%)	0 (0%)
Allergic Reaction	2 (10%)	0 (0%)
Allergy Aggravated	1 (5%)	0 (0%)
Alopecia	2 (10%)	0 (0%)
Altered Bowel Habit	1 (5%)	0 (0%)
Amblyopia	5 (24%)	0 (0%)
Amnesia	6 (29%)	0 (0%)
Anemia	3 (14%)	0 (0%)
Angina Pectoris	3 (14%)	0 (0%)
Anorexia	5 (24%)	0 (0%)
Anorgasmia	1 (5%)	0 (0%)
Anorgasmia Male	1 (5%)	0 (0%)
Anxiety	3 (14%)	0 (0%)
Apathy	1 (5%)	0 (0%)
Aphasia	1 (5%)	0 (0%)
Appetite Increased	1 (5%)	0 (0%)
Appl/Inj/Incision/Insert Site Infection/Inflam	1 (5%)	0 (0%)
Appl/Inj/Incision/Insertion Site Pain	1 (5%)	0 (0%)
Appl/Inj/Incision/Insertion Site Skin Necrosis	1 (5%)	0 (0%)
Arrhythmia	2 (10%)	0 (0%)
Arthralgia	6 (29%)	0 (0%)
Arthritis	5 (24%)	0 (0%)
Arthritis Aggravated	1 (5%)	0 (0%)
Arthrosis	4 (19%)	0 (0%)
Asthma	3 (14%)	0 (0%)
Atrial Fibrillation	1 (5%)	0 (0%)
Back Pain	6 (29%)	0 (0%)
Bladder Carcinoma	1 (5%)	0 (0%)
Blepharitis	1 (5%)	0 (0%)
Blood In Stool	1 (5%)	0 (0%)
Body Odor	1 (5%)	0 (0%)
Bone Disorder	1 (5%)	0 (0%)
Bone Fracture Accidental	1 (5%)	0 (0%)
Bone Pain	1 (5%)	0 (0%)
Breast Neoplasm	2 (10%)	0 (0%)
Breast Neoplasm Female	1 (5%)	0 (0%)
Breast Pain	3 (14%)	0 (0%)

Breast Pain Female	1 (5%)	0 (0%)
Bronchitis	5 (24%)	0 (0%)
Bronchospasm Aggravated	1 (5%)	0 (0%)
Bruise	1 (5%)	0 (0%)
Bun Increased	2 (10%)	0 (0%)
Bursitis	1 (5%)	0 (0%)
Carcinoma Of Lung	1 (5%)	0 (0%)
Cardiac Arrest	1 (5%)	0 (0%)
Cardiac Failure	1 (5%)	0 (0%)
Cardiovascular Disorder	2 (10%)	0 (0%)
Cataract Specified	1 (5%)	0 (0%)
Cellulitis	3 (14%)	0 (0%)
Cellulitis, Other Than Injection Site	1 (5%)	0 (0%)
Cerebrovascular Accident	2 (10%)	0 (0%)
Cerebrovascular Disorder	1 (5%)	0 (0%)
Cheilitis	1 (5%)	0 (0%)
Chest Pain	5 (24%)	0 (0%)
Chills	3 (14%)	0 (0%)
Chills And Fever	1 (5%)	0 (0%)
Cholecystitis	1 (5%)	0 (0%)
Cholelithiasis	1 (5%)	0 (0%)
Chronic Lymphocytic Leukemia	1 (5%)	0 (0%)
Circumoral Paresthesia	2 (10%)	0 (0%)
Colitis	3 (14%)	0 (0%)
Congenital Anomaly	1 (5%)	0 (0%)
Congestive Heart Failure	3 (14%)	0 (0%)
Conjunctivitis	5 (24%)	0 (0%)
Contact Dermatitis	1 (5%)	0 (0%)
Coordination Abnormal	1 (5%)	0 (0%)
Coronary Artery Disorder	1 (5%)	0 (0%)
Coronary Occlusion	1 (5%)	0 (0%)
Cough Increased	5 (24%)	0 (0%)
Coughing	1 (5%)	0 (0%)
Creatinine Blood Increased	1 (5%)	0 (0%)
Creatinine Increased	1 (5%)	0 (0%)
Cyst	2 (10%)	0 (0%)
Cystitis	1 (5%)	0 (0%)
Deafness	2 (10%)	0 (0%)
Deep Thrombophlebitis	1 (5%)	0 (0%)
Depersonalization	3 (14%)	0 (0%)
Depression	5 (24%)	0 (0%)
Dermatitis	1 (5%)	0 (0%)
Dermatitis Contact	1 (5%)	0 (0%)
Dermatitis Fungal	1 (5%)	0 (0%)
Diabetes Mellitus	3 (14%)	0 (0%)
Diabetes Mellitus Aggravated	1 (5%)	0 (0%)
Diplopia	5 (24%)	0 (0%)
Diverticulitis	1 (5%)	0 (0%)
Diverticulosis	1 (5%)	0 (0%)

Dry Eyes	1 (5%)	0 (0%)
Dry Skin	3 (14%)	0 (0%)
Duodenal Ulcer	1 (5%)	0 (0%)
Dysarthria	1 (5%)	0 (0%)
Dyspepsia	6 (29%)	0 (0%)
Dysphonia	1 (5%)	0 (0%)
Dyspnea	6 (29%)	0 (0%)
Dysuria	2 (10%)	0 (0%)
Ear Disorder	2 (10%)	0 (0%)
Ear Pain	4 (19%)	0 (0%)
Earache	1 (5%)	0 (0%)
Ecchymosis	5 (24%)	0 (0%)
Eczema	1 (5%)	0 (0%)
Edema	4 (19%)	0 (0%)
Edema Generalized	1 (5%)	0 (0%)
Emotional Lability	3 (14%)	0 (0%)
Encephalitis	1 (5%)	0 (0%)
Encephalopathy	1 (5%)	0 (0%)
Enteritis	1 (5%)	0 (0%)
Epistaxis	2 (10%)	0 (0%)
Eructation	1 (5%)	0 (0%)
Esophageal Ulcer	1 (5%)	0 (0%)
Esophageal Ulceration	1 (5%)	0 (0%)
Euphoria	1 (5%)	0 (0%)
Event Unevaluable	1 (5%)	0 (0%)
Extrapyramidal Syndrome	1 (5%)	0 (0%)
Eye Disorder	4 (19%)	0 (0%)
Eye Hemorrhage	1 (5%)	0 (0%)
Eye Pain	4 (19%)	0 (0%)
Face Edema	4 (19%)	0 (0%)
Facial Paralysis	1 (5%)	0 (0%)
Fecal Impaction	1 (5%)	0 (0%)
Fecal Incontinence	1 (5%)	0 (0%)
Fever	3 (14%)	0 (0%)
Fibrillation Atrial	1 (5%)	0 (0%)
Flank Pain	1 (5%)	0 (0%)
Flatulence	5 (24%)	0 (0%)
Flushing	1 (5%)	0 (0%)
Fungal Dermatitis	2 (10%)	0 (0%)
Furunculosis	2 (10%)	0 (0%)
Gastric Dilatation	1 (5%)	0 (0%)
Gastritis	2 (10%)	0 (0%)
Gastroenteritis	3 (14%)	0 (0%)
Gastroesophageal Reflux	1 (5%)	0 (0%)
Gastrointestinal Disorder	5 (24%)	0 (0%)
Generalized Edema	3 (14%)	0 (0%)
Gingival Bleeding	1 (5%)	0 (0%)
Gingivitis	2 (10%)	0 (0%)
Glucose Tolerance Decreased	1 (5%)	0 (0%)

Gout	2 (10%)	0 (0%)
Gum Hemorrhage	1 (5%)	0 (0%)
Gynecomastia	1 (5%)	0 (0%)
Hair Disorder	1 (5%)	0 (0%)
Hearing Decreased	1 (5%)	0 (0%)
Heart Arrest	1 (5%)	0 (0%)
Heart Failure	2 (10%)	0 (0%)
Hematuria	1 (5%)	0 (0%)
Hemoptysis	3 (14%)	0 (0%)
Hemorrhage	1 (5%)	0 (0%)
Hepatic Enzymes Increased	1 (5%)	0 (0%)
Hepatic Function Abnormal	1 (5%)	0 (0%)
Hepatitis Infectious	1 (5%)	0 (0%)
Hernia	2 (10%)	0 (0%)
Herpes Simplex	4 (19%)	0 (0%)
Herpes Zoster	3 (14%)	0 (0%)
Hiccup	1 (5%)	0 (0%)
Hot Flushes	1 (5%)	0 (0%)
Hypercholesterolemia	1 (5%)	0 (0%)
Hyperesthesia	1 (5%)	0 (0%)
Hyperglycemia	6 (29%)	0 (0%)
Hyperlipidemia	1 (5%)	0 (0%)
Hyperostosis	1 (5%)	0 (0%)
Hypertension	4 (19%)	0 (0%)
Hypertension Aggravated	1 (5%)	0 (0%)
Hypertonia	3 (14%)	0 (0%)
Hypesthesia	6 (29%)	0 (0%)
Hypoacusis	1 (5%)	0 (0%)
Hypoesthesia	1 (5%)	0 (0%)
Hypoglycemia	3 (14%)	0 (0%)
Hypokinesia	1 (5%)	0 (0%)
Hypothyroidism	1 (5%)	0 (0%)
Ileitis	1 (5%)	0 (0%)
Impotence	4 (19%)	0 (0%)
Incoordination	5 (24%)	0 (0%)
Increased Appetite	4 (19%)	0 (0%)
Increased Capillary Fragility	1 (5%)	0 (0%)
Infection Bacterial	1 (5%)	0 (0%)
Infection Tbc	1 (5%)	0 (0%)
Influenza-Like Symptoms	1 (5%)	0 (0%)
Insomnia	6 (29%)	0 (0%)
Intestinal Obstruction	1 (5%)	0 (0%)
Intestinal Ulcer	1 (5%)	0 (0%)
Irritability	1 (5%)	0 (0%)
Irritable Bowel Syndrome	1 (5%)	0 (0%)
Joint Disorder	2 (10%)	0 (0%)
Kidney Calculus	2 (10%)	0 (0%)
Kidney Pain	1 (5%)	0 (0%)
Lab Test Abnormal	2 (10%)	0 (0%)

Labile Blood Pressure	1 (5%)	0 (0%)
Lacrimation Disorder	1 (5%)	0 (0%)
Lactic Dehydrogenase Increased	2 (10%)	0 (0%)
LDH Increased	1 (5%)	0 (0%)
Leg Cramps	5 (24%)	0 (0%)
Libido Decreased	2 (10%)	0 (0%)
Libido Increased	1 (5%)	0 (0%)
Liver Fatty	1 (5%)	0 (0%)
Liver Fatty Deposit	1 (5%)	0 (0%)
Liver Function Tests Abnormal	3 (14%)	0 (0%)
Lung Disorder	2 (10%)	0 (0%)
Lymphadenopathy	2 (10%)	0 (0%)
Lymphadenopathy Cervical	1 (5%)	0 (0%)
Maculopapular Rash	1 (5%)	0 (0%)
Malabsorption Syndrome	1 (5%)	0 (0%)
Malaise	3 (14%)	0 (0%)
Melena	1 (5%)	0 (0%)
Micturition Disorder	1 (5%)	0 (0%)
Micturition Frequency	1 (5%)	0 (0%)
Migraine	3 (14%)	0 (0%)
Migraine Aggravated	1 (5%)	0 (0%)
Motor Vehicle Accident	1 (5%)	0 (0%)
Mouth Dry	1 (5%)	0 (0%)
Mouth Ulceration	2 (10%)	0 (0%)
Movement Disorder	2 (10%)	0 (0%)
Mucous Membrane Disorder	1 (5%)	0 (0%)
Muscle Contractions Involuntary	1 (5%)	0 (0%)
Muscle Cramps	1 (5%)	0 (0%)
Muscle Weakness	1 (5%)	0 (0%)
Muscular Hypertonia	1 (5%)	0 (0%)
Myalgia	6 (29%)	0 (0%)
Myasthenia	5 (24%)	0 (0%)
Myocardial Infarct	2 (10%)	0 (0%)
Myocardial Ischemia	1 (5%)	0 (0%)
Myoclonus	1 (5%)	0 (0%)
Myopia	1 (5%)	0 (0%)
Nail Disorder	1 (5%)	0 (0%)
Nausea Vomiting And Diarrhea	1 (5%)	0 (0%)
Neck Pain	4 (19%)	0 (0%)
Neoplasm	2 (10%)	0 (0%)
Nephritis	1 (5%)	0 (0%)
Nervousness	6 (29%)	0 (0%)
Neuralgia	2 (10%)	0 (0%)
Neuropathy	4 (19%)	0 (0%)
Nocturia	3 (14%)	0 (0%)
Nystagmus	1 (5%)	0 (0%)
Oral Moniliasis	3 (14%)	0 (0%)
Other And Unspecified Neoplasms	1 (5%)	0 (0%)
Other Lab Abnormality	1 (5%)	0 (0%)

Other Sexual Dysfunction Male	1 (5%)	0 (0%)
Otitis Media	6 (29%)	0 (0%)
Palpitation	4 (19%)	0 (0%)
Pancreatitis	2 (10%)	0 (0%)
Paralysis	1 (5%)	0 (0%)
Paranoid Reaction	1 (5%)	0 (0%)
Paresthesia	4 (19%)	0 (0%)
Pelvic Pain	1 (5%)	0 (0%)
Penis Disorder	2 (10%)	0 (0%)
Periodontal Abscess	2 (10%)	0 (0%)
Peripheral Vascular Disorder	2 (10%)	0 (0%)
Pharyngitis	6 (29%)	0 (0%)
Phlebitis	1 (5%)	0 (0%)
Photophobia	1 (5%)	0 (0%)
Pneumonia	3 (14%)	0 (0%)
Polyuria	3 (14%)	0 (0%)
Prostatic Disorder	1 (5%)	0 (0%)
Prothrombin Decreased	1 (5%)	0 (0%)
Pruritus	6 (29%)	0 (0%)
Psoriasis	2 (10%)	0 (0%)
Psoriasis Aggravated	1 (5%)	0 (0%)
Purpura	1 (5%)	0 (0%)
Pyelonephritis	2 (10%)	0 (0%)
Pyuria	1 (5%)	0 (0%)
Rash	5 (24%)	0 (0%)
Rash Erythematous	1 (5%)	0 (0%)
Reaction Unevaluable	1 (5%)	0 (0%)
Rectal Disorder	2 (10%)	0 (0%)
Rectal Hemorrhage	2 (10%)	0 (0%)
Reflexes Decreased	1 (5%)	0 (0%)
Refraction Disorder	1 (5%)	0 (0%)
Renal Calculus	1 (5%)	0 (0%)
Renal Pain	1 (5%)	0 (0%)
Respiratory Disorder	1 (5%)	0 (0%)
Respiratory System	1 (5%)	0 (0%)
Respiratory Tract Infection	1 (5%)	0 (0%)
Retinal Disorder	1 (5%)	0 (0%)
Retinal Hemorrhage	1 (5%)	0 (0%)
Retinal Vascular Disorder	1 (5%)	0 (0%)
Retinal Vein Thrombosis	1 (5%)	0 (0%)
Rheumatoid Arthritis	1 (5%)	0 (0%)
Rhinitis	5 (24%)	0 (0%)
Salivary Duct Obstruction	1 (5%)	0 (0%)
Scrotal Edema	1 (5%)	0 (0%)
Sepsis	2 (10%)	0 (0%)
SGOT Increased	1 (5%)	0 (0%)
SGPT Increased	1 (5%)	0 (0%)
Sialolithiasis	1 (5%)	0 (0%)
Sinusitis	5 (24%)	0 (0%)

Skeletal Pain	1 (5%)	0 (0%)
Skin Benign Neoplasm	2 (10%)	0 (0%)
Skin Carcinoma	1 (5%)	0 (0%)
Skin Cold Clammy	1 (5%)	0 (0%)
Skin Discoloration	2 (10%)	0 (0%)
Skin Disorder	4 (19%)	0 (0%)
Skin Dry	1 (5%)	0 (0%)
Skin Ulcer	3 (14%)	0 (0%)
Skin Ulceration	1 (5%)	0 (0%)
Speech Disorder	4 (19%)	0 (0%)
Stomach Atony	1 (5%)	0 (0%)
Stomatitis	1 (5%)	0 (0%)
Stools Loose	1 (5%)	0 (0%)
Stupor	2 (10%)	0 (0%)
Sweating	6 (29%)	0 (0%)
Sweating Increased	1 (5%)	0 (0%)
Syncope	4 (19%)	0 (0%)
Synovitis	1 (5%)	0 (0%)
Tachycardia	2 (10%)	0 (0%)
Taste Loss	1 (5%)	0 (0%)
Taste Perversion	3 (14%)	0 (0%)
Tendinitis	1 (5%)	0 (0%)
Tendinous Contracture	1 (5%)	0 (0%)
Tenosynovitis	2 (10%)	0 (0%)
Thinking Abnormal	5 (24%)	0 (0%)
Thirst	5 (24%)	0 (0%)
Thrombocytopenia	1 (5%)	0 (0%)
Thrombophlebitis	1 (5%)	0 (0%)
Thrombophlebitis Leg Deep	1 (5%)	0 (0%)
Thrombosis	2 (10%)	0 (0%)
Thrombosis Coronary	1 (5%)	0 (0%)
Tinnitus	3 (14%)	0 (0%)
Tongue Disorder	1 (5%)	0 (0%)
Tooth Ache	1 (5%)	0 (0%)
Tooth Disorder	4 (19%)	0 (0%)
Tremor	4 (19%)	0 (0%)
Twitching	4 (19%)	0 (0%)
Urethral Pain	1 (5%)	0 (0%)
Urethral/Ureteral Disorder	1 (5%)	0 (0%)
Urinary Frequency	5 (24%)	0 (0%)
Urinary Incontinence	3 (14%)	0 (0%)
Urinary Retention	1 (5%)	0 (0%)
Urinary Tract Disorder	1 (5%)	0 (0%)
Urinary Tract Infection	5 (24%)	0 (0%)
Urinary Urgency	1 (5%)	0 (0%)
Urine Abnormality	1 (5%)	0 (0%)
Urticaria	1 (5%)	0 (0%)
Vascular Disorder	1 (5%)	0 (0%)
Vasodilatation	4 (19%)	0 (0%)

Verruca	1 (5%)	0 (0%)
Vesiculobullous Rash	4 (19%)	0 (0%)
Vestibular Disorder	1 (5%)	0 (0%)
Voice Alteration	2 (10%)	0 (0%)
Vomiting	6 (29%)	0 (0%)
Weight Decrease	1 (5%)	0 (0%)
Weight Gain	5 (24%)	0 (0%)
Weight Loss	2 (10%)	0 (0%)
Worsening Heart Failure	1 (5%)	0 (0%)
Xerophthalmia	1 (5%)	0 (0%)
Named serious adverse events		
Cardiac Failure Congestion	1 (5%)	1 (5%)
Cellulitis	2 (10%)	1 (5%)
Hematuria	1 (5%)	1 (5%)
Left Arm Fracture	1 (5%)	1 (5%)
Myocardial Infarction	1 (5%)	1 (5%)
Osteochondrosis	1 (5%)	1 (5%)
Pancoast Tumor	1 (5%)	1 (5%)
Pancreatitis Chronic	1 (5%)	1 (5%)
Thrombophlebitis	1 (5%)	1 (5%)
Abscess	1 (5%)	0 (0%)
Accidental Injury	4 (19%)	0 (0%)
Alkaline Phosphatase Increased	1 (5%)	0 (0%)
Angina Pectoris	2 (10%)	0 (0%)
Arthritis	1 (5%)	0 (0%)
Arthrosis	1 (5%)	0 (0%)
Asthenia	1 (5%)	0 (0%)
Back Pain	1 (5%)	0 (0%)
Bladder Carcinoma	1 (5%)	0 (0%)
Bone Disorder	1 (5%)	0 (0%)
Bone Fracture Accidental	1 (5%)	0 (0%)
Carcinoma Of Lung	1 (5%)	0 (0%)
Cardiac Arrest	1 (5%)	0 (0%)
Cardiac Failure	1 (5%)	0 (0%)
Cerebrovascular Accident	1 (5%)	0 (0%)
Cerebrovascular Disorder	1 (5%)	0 (0%)
Chest Pain	3 (14%)	0 (0%)
Cholecystitis	1 (5%)	0 (0%)
Cholelithiasis	1 (5%)	0 (0%)
Chronic Lymphocytic Leukemia	1 (5%)	0 (0%)
Congestive Heart Failure	2 (10%)	0 (0%)
Constipation	1 (5%)	0 (0%)
Coronary Artery Disorder	1 (5%)	0 (0%)
Death	1 (5%)	0 (0%)
Depression	2 (10%)	0 (0%)
Dizziness	1 (5%)	0 (0%)
Dyspnea	1 (5%)	0 (0%)
Encephalopathy	1 (5%)	0 (0%)
Fever	1 (5%)	0 (0%)

Glucose Tolerance Decreased	1 (5%)	0 (0%)
Headache	1 (5%)	0 (0%)
Hemoptysis	1 (5%)	0 (0%)
Hyperglycemia	1 (5%)	0 (0%)
Hypertension	1 (5%)	0 (0%)
Infection	1 (5%)	0 (0%)
Infection Tbc	1 (5%)	0 (0%)
Intestinal Obstruction	1 (5%)	0 (0%)
Maculopapular Rash	1 (5%)	0 (0%)
Malabsorption Syndrome	1 (5%)	0 (0%)
Motor Vehicle Accident	1 (5%)	0 (0%)
Myasthenia	1 (5%)	0 (0%)
Myocardial Infarct	2 (10%)	0 (0%)
Myocardial Ischemia	1 (5%)	0 (0%)
Nausea	1 (5%)	0 (0%)
Pancreatitis	2 (10%)	0 (0%)
Pneumonia	3 (14%)	0 (0%)
Pyelonephritis	1 (5%)	0 (0%)
Rectal Disorder	1 (5%)	0 (0%)
Retinal Vein Thrombosis	1 (5%)	0 (0%)
Skin Carcinoma	1 (5%)	0 (0%)
Skin Ulcer	1 (5%)	0 (0%)
Stomach Atony	1 (5%)	0 (0%)
Syncope	4 (19%)	0 (0%)
Thrombophlebitis Leg Deep	1 (5%)	0 (0%)
Thrombosis	1 (5%)	0 (0%)
Thrombosis Coronary	1 (5%)	0 (0%)
Vertigo	1 (5%)	0 (0%)
Vomiting	2 (10%)	0 (0%)
Worsening Heart Failure	1 (5%)	0 (0%)

Appendix Table 2-3. Quetiapine trials with data that could be included in a meta-analysis, by whether the data source is public

Appendix Table 2-3 Legend: For example, when including data from any source, 3/7 (43%) trials reported meta-analyzable results for the number of participants who experienced anxiety. When including only data from public sources, 1/7 (14%) trials reported meta-analyzable results for the number of participants who experienced anxiety.

The first section of the table includes the number of participants experiencing any AE(s) and the number of participants experiencing any serious AE(s).

The second section of the table includes specific adverse events (in alphabetical order) for which meta-analyzable data were reported in a public source for at least one trial, followed by specific adverse events (in alphabetical order) for which meta-analyzable data were not reported in any public sources.

The third section of the table includes specific serious adverse events (in alphabetical order) for which meta-analyzable data were reported in a public source for at least one trial, followed by specific serious adverse events (in alphabetical order) for which meta-analyzable data were not reported in any public sources.

	Quetiapine for bipolar depression (N=7 trials)	
	Trials with meta-analyzable data across all sources No. (%)	**Trials with meta-analyzable data across public sources No. (%)**
Aggregated adverse events		
No. participants experiencing ≥1 AE	6 (86%)	3 (43%)
No. participants experiencing ≥1 serious AE	5 (71%)	4 (57%)
Named adverse events		
Anxiety	3 (43%)	1 (14%)
Appetite Decrease	2 (29%)	1 (14%)
Appetite Increase	4 (57%)	3 (43%)
Constipation	5 (71%)	5 (71%)
Diarrhea	4 (57%)	3 (43%)
Dizziness	6 (86%)	6 (86%)
Dry Mouth	6 (86%)	6 (86%)
Dyspepsia	4 (57%)	2 (29%)
Fatigue	4 (57%)	4 (57%)
Headache	6 (86%)	6 (86%)
Hypomania	3 (43%)	1 (14%)
Insomnia	5 (71%)	3 (43%)
Light-Headed	1 (14%)	1 (14%)
Nasopharyngitis	3 (43%)	1 (14%)
Nausea	6 (86%)	6 (86%)
Sedation	6 (86%)	6 (86%)
Somnolence	5 (71%)	5 (71%)
Stomach Upset	1 (14%)	1 (14%)
Tremor	3 (43%)	1 (14%)
Upper Respiratory Tract Infection	2 (29%)	1 (14%)
Weight Gain	1 (14%)	1 (14%)
Abdominal Discomfort	2 (29%)	0 (0%)
Abdominal Distension	2 (29%)	0 (0%)

Abdominal Pain	1 (14%)	0 (0%)
Abdominal Pain Lower	2 (29%)	0 (0%)
Abdominal Pain NOS	1 (14%)	0 (0%)
Abdominal Pain Upper	2 (29%)	0 (0%)
Abdominal Tenderness	1 (14%)	0 (0%)
Abnormal Dreams	2 (29%)	0 (0%)
Accidental Overdose	2 (29%)	0 (0%)
Acne	1 (14%)	0 (0%)
Acne NOS	1 (14%)	0 (0%)
Acute Myocardial Infarction	1 (14%)	0 (0%)
Acute Psychosis	1 (14%)	0 (0%)
Adnexa Uteri Pain	1 (14%)	0 (0%)
Aggression	1 (14%)	0 (0%)
Agitation	2 (29%)	0 (0%)
Akathisia	2 (29%)	0 (0%)
Alcohol Intolerance	1 (14%)	0 (0%)
Alopecia	2 (29%)	0 (0%)
Altered Visual Depth Perception	2 (29%)	0 (0%)
Amnesia	2 (29%)	0 (0%)
Anemia	1 (14%)	0 (0%)
Anger	2 (29%)	0 (0%)
Anorexia	1 (14%)	0 (0%)
Anorgasmia	1 (14%)	0 (0%)
Aphasia	1 (14%)	0 (0%)
Aphthous Stomatitis	1 (14%)	0 (0%)
Appetite Decrease NOS	1 (14%)	0 (0%)
Appetite Increase NOS	1 (14%)	0 (0%)
Aptyalism	1 (14%)	0 (0%)
Arthralgia	2 (29%)	0 (0%)
Arthritis NOS	1 (14%)	0 (0%)
Arthropod Bite	2 (29%)	0 (0%)
Arthropod Sting	1 (14%)	0 (0%)
Asthenia	2 (29%)	0 (0%)
Asthma NOS	1 (14%)	0 (0%)
Astigmatism	1 (14%)	0 (0%)
Ataxia	2 (29%)	0 (0%)
Atrioventricular Block First Degree	1 (14%)	0 (0%)
Back Injury	1 (14%)	0 (0%)
Back Injury NOS	1 (14%)	0 (0%)
Back Pain	2 (29%)	0 (0%)
Balance Disorder	1 (14%)	0 (0%)
Balance Impaired NOS	1 (14%)	0 (0%)
Bipolar Disorder	1 (14%)	0 (0%)
Bipolar I Disorder	2 (29%)	0 (0%)
Bladder Disorder NOS	1 (14%)	0 (0%)
Blepharitis	1 (14%)	0 (0%)
Blepharospasm	1 (14%)	0 (0%)
Blood In Stool	1 (14%)	0 (0%)
Blood Pressure Increased	1 (14%)	0 (0%)

Blood Pressure Systolic Increased	1 (14%)	0 (0%)
Blood Triglycerides Increased	1 (14%)	0 (0%)
Blood Urine	1 (14%)	0 (0%)
Blunted Affect	1 (14%)	0 (0%)
Body Temperature Increased	1 (14%)	0 (0%)
Bradycardia	1 (14%)	0 (0%)
Bradyphrenia	1 (14%)	0 (0%)
Breast Cyst	1 (14%)	0 (0%)
Breast Tenderness	1 (14%)	0 (0%)
Bronchitis	1 (14%)	0 (0%)
Bronchitis NOS	1 (14%)	0 (0%)
Bronchospasm NOS	1 (14%)	0 (0%)
Bruxism	2 (29%)	0 (0%)
Buttock Pain	1 (14%)	0 (0%)
Carpal Tunnel Syndrome	1 (14%)	0 (0%)
Cerumen Impaction	1 (14%)	0 (0%)
Chapped Lips	1 (14%)	0 (0%)
Cheilitis	1 (14%)	0 (0%)
Chemical Injury	1 (14%)	0 (0%)
Chest Discomfort	2 (29%)	0 (0%)
Chest Pain	2 (29%)	0 (0%)
Chest Tightness	1 (14%)	0 (0%)
Chest Wall Pain	2 (29%)	0 (0%)
Chills	1 (14%)	0 (0%)
Chlamydial Infection	1 (14%)	0 (0%)
Choking Sensation	1 (14%)	0 (0%)
Cholecystitis NOS	1 (14%)	0 (0%)
Chronic Lymphocytic Leukemia NOS	1 (14%)	0 (0%)
Chronic Obstructive Airways Disease	1 (14%)	0 (0%)
Cognitive Disorder	1 (14%)	0 (0%)
Confusional State	2 (29%)	0 (0%)
Conjunctival Hyperemia	1 (14%)	0 (0%)
Conjunctivitis Infective	1 (14%)	0 (0%)
Constricted Affect	1 (14%)	0 (0%)
Contusion	2 (29%)	0 (0%)
Conversion Disorder	1 (14%)	0 (0%)
Convulsion	1 (14%)	0 (0%)
Convulsions NOS	1 (14%)	0 (0%)
Coordination Abnormal	1 (14%)	0 (0%)
Coordination Abnormal NOS	1 (14%)	0 (0%)
Corneal Abrasion	1 (14%)	0 (0%)
Cough	2 (29%)	0 (0%)
Decreased Immune Responsiveness	1 (14%)	0 (0%)
Deep Vein Thrombosis	1 (14%)	0 (0%)
Delusion NOS	1 (14%)	0 (0%)
Depression	2 (29%)	0 (0%)
Derealization	1 (14%)	0 (0%)
Dermatitis Allergic	1 (14%)	0 (0%)
Dermatitis Contact	1 (14%)	0 (0%)

Dermatitis Exfoliative NOS	1 (14%)	0 (0%)
Diarrhea NOS	1 (14%)	0 (0%)
Difficulty In Walking	1 (14%)	0 (0%)
Diplopia	1 (14%)	0 (0%)
Disorientation	2 (29%)	0 (0%)
Dissociation	1 (14%)	0 (0%)
Dissociative Disorder NOS	1 (14%)	0 (0%)
Disturbance In Attention	2 (29%)	0 (0%)
Dizziness Postural	2 (29%)	0 (0%)
Drug Abuser NOS	1 (14%)	0 (0%)
Drug Hypersensitivity	1 (14%)	0 (0%)
Drug Withdrawal Syndrome	1 (14%)	0 (0%)
Dry Eye	1 (14%)	0 (0%)
Dry Eye NOS	1 (14%)	0 (0%)
Dry Skin	1 (14%)	0 (0%)
Dry Throat	1 (14%)	0 (0%)
Duodenal Ulcer Hemorrhage	1 (14%)	0 (0%)
Dupuytren's Contracture	1 (14%)	0 (0%)
Dysarthria	2 (29%)	0 (0%)
Dysgeusia	2 (29%)	0 (0%)
Dyskinesia	2 (29%)	0 (0%)
Dysmenorrhea	2 (29%)	0 (0%)
Dysphagia	2 (29%)	0 (0%)
Dysphemia	1 (14%)	0 (0%)
Dyspnea	2 (29%)	0 (0%)
Dystonia	2 (29%)	0 (0%)
Dysuria	2 (29%)	0 (0%)
Ear Congestion	2 (29%)	0 (0%)
Ear Discomfort	1 (14%)	0 (0%)
Ear Infection	1 (14%)	0 (0%)
Ear Infection NOS	1 (14%)	0 (0%)
Ear Infection Viral NOS	1 (14%)	0 (0%)
Ear Pain	2 (29%)	0 (0%)
Ear Pruritus	1 (14%)	0 (0%)
Ecchymosis	1 (14%)	0 (0%)
Ectopic Pregnancy	1 (14%)	0 (0%)
Edema Peripheral	2 (29%)	0 (0%)
Ejaculation Delayed	1 (14%)	0 (0%)
Elevated Mood	1 (14%)	0 (0%)
Enuresis	1 (14%)	0 (0%)
Epistaxis	2 (29%)	0 (0%)
Erectile Dysfunction	1 (14%)	0 (0%)
Erectile Dysfunction NOS	1 (14%)	0 (0%)
Eructation	1 (14%)	0 (0%)
Erythema	1 (14%)	0 (0%)
Esophageal Spasm	1 (14%)	0 (0%)
Euphoric Mood	1 (14%)	0 (0%)
Excoriation	1 (14%)	0 (0%)
Extrapyramidal Disorder	2 (29%)	0 (0%)

Eye Pain	1 (14%)	0 (0%)
Eye Redness	1 (14%)	0 (0%)
Eye Swelling	1 (14%)	0 (0%)
Eyelids Pruritus	1 (14%)	0 (0%)
Facial Pain	1 (14%)	0 (0%)
Factor Ii Deficiency	1 (14%)	0 (0%)
Feces Hard	1 (14%)	0 (0%)
Feeling Abnormal	1 (14%)	0 (0%)
Feeling Cold	1 (14%)	0 (0%)
Feeling Hot	2 (29%)	0 (0%)
Feeling Hot And Cold	1 (14%)	0 (0%)
Feeling Jittery	2 (29%)	0 (0%)
Fibula Fracture	1 (14%)	0 (0%)
Flank Pain	2 (29%)	0 (0%)
Flat Affect	2 (29%)	0 (0%)
Flatulence	2 (29%)	0 (0%)
Fluid Retention	1 (14%)	0 (0%)
Flushing	2 (29%)	0 (0%)
Food Craving	2 (29%)	0 (0%)
Food Poisoning	1 (14%)	0 (0%)
Food Poisoning NOS	1 (14%)	0 (0%)
Foot Fracture	1 (14%)	0 (0%)
Fractured Coccyx	1 (14%)	0 (0%)
Frequent Bowel Movements	1 (14%)	0 (0%)
Fungal Infection NOS	1 (14%)	0 (0%)
Gait Abnormal	1 (14%)	0 (0%)
Gait Disturbance	1 (14%)	0 (0%)
Gastritis	1 (14%)	0 (0%)
Gastroenteritis	1 (14%)	0 (0%)
Gastroenteritis Viral	1 (14%)	0 (0%)
Gastroenteritis Viral NOS	1 (14%)	0 (0%)
Gastroesophageal Reflux Disease	2 (29%)	0 (0%)
Gastrointestinal Pain NOS	1 (14%)	0 (0%)
Gingival Infection	1 (14%)	0 (0%)
Gingival Pain	2 (29%)	0 (0%)
Glossodynia	2 (29%)	0 (0%)
Gout	1 (14%)	0 (0%)
Groin Pain	1 (14%)	0 (0%)
Haemorrhoids	1 (14%)	0 (0%)
Hallucination	1 (14%)	0 (0%)
Hallucination, Auditory	2 (29%)	0 (0%)
Hallucination, Visual	2 (29%)	0 (0%)
Hand Fracture	1 (14%)	0 (0%)
Hangover	1 (14%)	0 (0%)
Heart Rate Increased	1 (14%)	0 (0%)
Heart Rate Irregular	1 (14%)	0 (0%)
Hematoma NOS	1 (14%)	0 (0%)
Hemiparesis	1 (14%)	0 (0%)
Hemorrhoids	1 (14%)	0 (0%)

Hernia NOS	1 (14%)	0 (0%)
Herpes Simplex	2 (29%)	0 (0%)
Hiccups	1 (14%)	0 (0%)
Hip Fracture	1 (14%)	0 (0%)
Hoarseness	1 (14%)	0 (0%)
Hostility	1 (14%)	0 (0%)
Hot Flush	1 (14%)	0 (0%)
Hyperacusis	1 (14%)	0 (0%)
Hyperglycemia	1 (14%)	0 (0%)
Hyperhidrosis	1 (14%)	0 (0%)
Hyperkeratosis	1 (14%)	0 (0%)
Hyperreflexia	1 (14%)	0 (0%)
Hypersensitivity	1 (14%)	0 (0%)
Hypersensitivity NOS	1 (14%)	0 (0%)
Hypersomnia	2 (29%)	0 (0%)
Hypertension	1 (14%)	0 (0%)
Hypertension NOS	1 (14%)	0 (0%)
Hypnagogic Hallucination	1 (14%)	0 (0%)
Hypoesthesia	2 (29%)	0 (0%)
Hypoesthesia Oral	1 (14%)	0 (0%)
Hyporeflexia	1 (14%)	0 (0%)
Hypotension NOS	1 (14%)	0 (0%)
Hypothyroidism	1 (14%)	0 (0%)
Illusion	1 (14%)	0 (0%)
Increased Tendency To Bruise	1 (14%)	0 (0%)
Infected Insect Bite	1 (14%)	0 (0%)
Influenza	2 (29%)	0 (0%)
Influenza Like Illness	2 (29%)	0 (0%)
Initial Insomnia	1 (14%)	0 (0%)
Injury	1 (14%)	0 (0%)
Intervertebral Disc Herniation	1 (14%)	0 (0%)
Intestinal Obstruction NOS	1 (14%)	0 (0%)
Irritability	2 (29%)	0 (0%)
Irritable Bowel Syndrome	2 (29%)	0 (0%)
Joint Dislocation	1 (14%)	0 (0%)
Joint Sprain	2 (29%)	0 (0%)
Joint Stiffness	1 (14%)	0 (0%)
Joint Swelling	1 (14%)	0 (0%)
Kidney Infection NOS	1 (14%)	0 (0%)
Lacrimation Increased	1 (14%)	0 (0%)
Laryngeal Edema	1 (14%)	0 (0%)
Laryngitis NOS	1 (14%)	0 (0%)
Lethargy	2 (29%)	0 (0%)
Libido Decreased	2 (29%)	0 (0%)
Libido Increased	2 (29%)	0 (0%)
Limb Discomfort NOS	1 (14%)	0 (0%)
Limb Injury NOS	1 (14%)	0 (0%)
Localized Infection	1 (14%)	0 (0%)
Logorrhea	2 (29%)	0 (0%)

Loose Stools	1 (14%)	0 (0%)
Loss Of Libido	2 (29%)	0 (0%)
Lymphadenopathy	1 (14%)	0 (0%)
Major Depressive Disorder NOS	1 (14%)	0 (0%)
Malaise	1 (14%)	0 (0%)
Mania	2 (29%)	0 (0%)
Memory Impairment	2 (29%)	0 (0%)
Menorrhagia	1 (14%)	0 (0%)
Menses Delayed	1 (14%)	0 (0%)
Menstruation Irregular	2 (29%)	0 (0%)
Mental Impairment NOS	1 (14%)	0 (0%)
Mental Status Changes	1 (14%)	0 (0%)
Micturition Urgency	2 (29%)	0 (0%)
Middle Insomnia	1 (14%)	0 (0%)
Migraine	1 (14%)	0 (0%)
Migraine NOS	1 (14%)	0 (0%)
Mitral Valve Prolapse	1 (14%)	0 (0%)
Mood Swings	1 (14%)	0 (0%)
Mucous Membrane Disorder NOS	1 (14%)	0 (0%)
Muscle Contractions Involuntary	1 (14%)	0 (0%)
Muscle Cramp	2 (29%)	0 (0%)
Muscle Rigidity	1 (14%)	0 (0%)
Muscle Spasms	2 (29%)	0 (0%)
Muscle Stiffness	1 (14%)	0 (0%)
Muscle Strain	2 (29%)	0 (0%)
Muscle Tightness	2 (29%)	0 (0%)
Muscle Twitching	2 (29%)	0 (0%)
Muscle Weakness NOS	1 (14%)	0 (0%)
Musculoskeletal Discomfort	1 (14%)	0 (0%)
Musculoskeletal Pain	1 (14%)	0 (0%)
Musculoskeletal Stiffness	2 (29%)	0 (0%)
Myalgia	2 (29%)	0 (0%)
Myoclonus	1 (14%)	0 (0%)
Nasal Congestion	2 (29%)	0 (0%)
Nasal Dryness	2 (29%)	0 (0%)
Nasal Edema	1 (14%)	0 (0%)
Neck Pain	1 (14%)	0 (0%)
Nephrolithiasis	1 (14%)	0 (0%)
Nervousness	2 (29%)	0 (0%)
Night Sweats	2 (29%)	0 (0%)
Nightmare	2 (29%)	0 (0%)
Nipple Exudate Bloody	1 (14%)	0 (0%)
Nocturia	1 (14%)	0 (0%)
Non-Accidental Overdose	1 (14%)	0 (0%)
Non-Cardiac Chest Pain	1 (14%)	0 (0%)
Obsessive-Compulsive Disorder	2 (29%)	0 (0%)
Onychophagia	1 (14%)	0 (0%)
Oral Pain	1 (14%)	0 (0%)
Orthostatic Hypotension	2 (29%)	0 (0%)

Osteoarthritis	1 (14%)	0 (0%)
Otitis Externa	1 (14%)	0 (0%)
Otitis Externa NOS	1 (14%)	0 (0%)
Otitis Media NOS	1 (14%)	0 (0%)
Pain	1 (14%)	0 (0%)
Pain In Extremity	2 (29%)	0 (0%)
Pain NOS	1 (14%)	0 (0%)
Palpitations	2 (29%)	0 (0%)
Pancreatitis NOS	1 (14%)	0 (0%)
Panic Attack	2 (29%)	0 (0%)
Panic Disorder NOS	1 (14%)	0 (0%)
Paranoia	2 (29%)	0 (0%)
Paresthesia	2 (29%)	0 (0%)
Paresthesia Oral	1 (14%)	0 (0%)
Periarthritis	1 (14%)	0 (0%)
Periorbital Hematoma	1 (14%)	0 (0%)
Pharyngeal Erythema	1 (14%)	0 (0%)
Pharyngitis	1 (14%)	0 (0%)
Pharyngitis Streptococcal	2 (29%)	0 (0%)
Pharyngolaryngeal Pain	2 (29%)	0 (0%)
Photophobia	2 (29%)	0 (0%)
Photopsia	1 (14%)	0 (0%)
Photosensitivity Reaction	1 (14%)	0 (0%)
Pitting Edema	1 (14%)	0 (0%)
Pneumonia	1 (14%)	0 (0%)
Pollakiuria	2 (29%)	0 (0%)
Polymenorrhea	1 (14%)	0 (0%)
Polymyalgia	1 (14%)	0 (0%)
Post Procedural Complication	1 (14%)	0 (0%)
Post Procedural Pain	2 (29%)	0 (0%)
Productive Cough	1 (14%)	0 (0%)
Prostate Infection	1 (14%)	0 (0%)
Prostatitis	1 (14%)	0 (0%)
Pruritus	2 (29%)	0 (0%)
Pruritus Generalized	1 (14%)	0 (0%)
Psychomotor Hyperactivity	1 (14%)	0 (0%)
Psychomotor Retardation	1 (14%)	0 (0%)
Pulmonary Congestion	1 (14%)	0 (0%)
Pyrexia	2 (29%)	0 (0%)
Rash	1 (14%)	0 (0%)
Rash NOS	1 (14%)	0 (0%)
Rash Pruritic	1 (14%)	0 (0%)
Respiratory Tract Congestion	1 (14%)	0 (0%)
Respiratory Tract Infection	1 (14%)	0 (0%)
Restless Legs Syndrome	2 (29%)	0 (0%)
Restlessness	2 (29%)	0 (0%)
Retching	1 (14%)	0 (0%)
Rhinitis	1 (14%)	0 (0%)
Rhinorrhea	1 (14%)	0 (0%)

Rib Fracture	1 (14%)	0 (0%)
Rigors	1 (14%)	0 (0%)
Salivary Hypersecretion	1 (14%)	0 (0%)
Scabies Infestation	1 (14%)	0 (0%)
Sciatica	1 (14%)	0 (0%)
Scratch	1 (14%)	0 (0%)
Seasonal Allergy	2 (29%)	0 (0%)
Self Esteem Inflated	1 (14%)	0 (0%)
Sensation Of Blood Flow	1 (14%)	0 (0%)
Sensation Of Heaviness	2 (29%)	0 (0%)
Sensation Of Pressure In Ear	1 (14%)	0 (0%)
Sensory Disturbance NOS	1 (14%)	0 (0%)
Sexual Dysfunction	1 (14%)	0 (0%)
Sexual Dysfunction NOS	1 (14%)	0 (0%)
Sialoadenitis NOS	1 (14%)	0 (0%)
Sinus Congestion	2 (29%)	0 (0%)
Sinus Headache	2 (29%)	0 (0%)
Sinus Pain	2 (29%)	0 (0%)
Sinusitis	1 (14%)	0 (0%)
Sinusitis NOS	1 (14%)	0 (0%)
Skin Irritation	1 (14%)	0 (0%)
Skin Laceration	2 (29%)	0 (0%)
Skin Lesion NOS	1 (14%)	0 (0%)
Skin Ulcer	1 (14%)	0 (0%)
Sleep Disorder	1 (14%)	0 (0%)
Sleep Talking	1 (14%)	0 (0%)
Sleep Walking	1 (14%)	0 (0%)
Sluggishness	2 (29%)	0 (0%)
Speech Disorder	1 (14%)	0 (0%)
Spinal Fracture NOS	1 (14%)	0 (0%)
Staphylococcal Infection	1 (14%)	0 (0%)
Stomach Discomfort	1 (14%)	0 (0%)
Stomatitis	1 (14%)	0 (0%)
Streptococcal Infection	1 (14%)	0 (0%)
Stress Symptoms	1 (14%)	0 (0%)
Subcutaneous Nodule	1 (14%)	0 (0%)
Suicidal Ideation	2 (29%)	0 (0%)
Suicide Attempt	2 (29%)	0 (0%)
Sunburn	1 (14%)	0 (0%)
Suspiciousness	1 (14%)	0 (0%)
Sweating Increased	1 (14%)	0 (0%)
Swollen Tongue	1 (14%)	0 (0%)
Syncope	2 (29%)	0 (0%)
Tachycardia	1 (14%)	0 (0%)
Tachycardia NOS	1 (14%)	0 (0%)
Tendonitis	1 (14%)	0 (0%)
Tension	1 (14%)	0 (0%)
Tension Headache	2 (29%)	0 (0%)
Thermal Burn	2 (29%)	0 (0%)

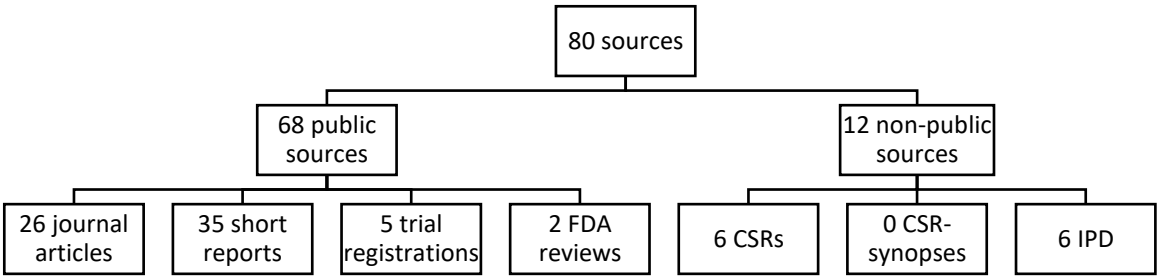
Thirst	2 (29%)	0 (0%)
Thought Blocking	1 (14%)	0 (0%)
Throat Tightness	2 (29%)	0 (0%)
Tinea Versicolor	1 (14%)	0 (0%)
Tinnitus	2 (29%)	0 (0%)
Tongue Coated	1 (14%)	0 (0%)
Tongue Disorder	1 (14%)	0 (0%)
Tongue Disorder NOS	1 (14%)	0 (0%)
Tonsillitis	1 (14%)	0 (0%)
Tooth Disorder NOS	1 (14%)	0 (0%)
Tooth Extraction	1 (14%)	0 (0%)
Tooth Extraction NOS	1 (14%)	0 (0%)
Tooth Infection	2 (29%)	0 (0%)
Tooth Injury	1 (14%)	0 (0%)
Tooth Loss	1 (14%)	0 (0%)
Toothache	2 (29%)	0 (0%)
Trismus	1 (14%)	0 (0%)
Upper Respiratory Tract Infection NOS	1 (14%)	0 (0%)
Urinary Hesitation	2 (29%)	0 (0%)
Urinary Incontinence	2 (29%)	0 (0%)
Urinary Retention	1 (14%)	0 (0%)
Urinary Tract Infection	1 (14%)	0 (0%)
Urinary Tract Infection NOS	1 (14%)	0 (0%)
Uterine Cyst	1 (14%)	0 (0%)
Uterine Fibroids	1 (14%)	0 (0%)
Uterine Spasm	1 (14%)	0 (0%)
Vaginosis Fungal NOS	1 (14%)	0 (0%)
Vasectomy	1 (14%)	0 (0%)
Ventricular Extrasystoles	1 (14%)	0 (0%)
Vertigo	2 (29%)	0 (0%)
Viral Infection	1 (14%)	0 (0%)
Viral Infection NOS	1 (14%)	0 (0%)
Viral Upper Respiratory Tract Infection	1 (14%)	0 (0%)
Vision Blurred	2 (29%)	0 (0%)
Visual Acuity Reduced	1 (14%)	0 (0%)
Visual Disturbance	1 (14%)	0 (0%)
Vomiting	1 (14%)	0 (0%)
Vomiting NOS	1 (14%)	0 (0%)
Weight Decreased	2 (29%)	0 (0%)
Weight Increased	2 (29%)	0 (0%)
Yawning	1 (14%)	0 (0%)
Named serious adverse events		
Depression	2 (29%)	1 (14%)
Accidental Overdose	1 (14%)	0 (0%)
Acute Myocardial Infarction	1 (14%)	0 (0%)
Acute Psychosis	1 (14%)	0 (0%)
Adnexa Uteri Pain	1 (14%)	0 (0%)
Asthma NOS	1 (14%)	0 (0%)
Bipolar I Disorder	2 (29%)	0 (0%)

Chest Pain	1 (14%)	0 (0%)
Cholecystitis NOS	1 (14%)	0 (0%)
Conversion Disorder	1 (14%)	0 (0%)
Convulsion	1 (14%)	0 (0%)
Convulsions NOS	1 (14%)	0 (0%)
Death	2 (29%)	0 (0%)
Deep Vein Thrombosis	1 (14%)	0 (0%)
Drug Hypersensitivity	1 (14%)	0 (0%)
Duodenal Ulcer Hemorrhage	1 (14%)	0 (0%)
Ectopic Pregnancy	1 (14%)	0 (0%)
Hallucination, Auditory	1 (14%)	0 (0%)
Hemiparesis	1 (14%)	0 (0%)
Hernia NOS	1 (14%)	0 (0%)
Hip Fracture	1 (14%)	0 (0%)
Influenza Like Illness	1 (14%)	0 (0%)
Injury	1 (14%)	0 (0%)
Intervertebral Disc Herniation	1 (14%)	0 (0%)
Intestinal Obstruction NOS	1 (14%)	0 (0%)
Major Depressive Disorder NOS	1 (14%)	0 (0%)
Mania	1 (14%)	0 (0%)
Mental Status Changes	1 (14%)	0 (0%)
Migraine NOS	1 (14%)	0 (0%)
Mitral Valve Prolapse	1 (14%)	0 (0%)
Non-Accidental Overdose	1 (14%)	0 (0%)
Pancreatitis NOS	1 (14%)	0 (0%)
Prostatitis	1 (14%)	0 (0%)
Spinal Fracture NOS	1 (14%)	0 (0%)
Suicidal Ideation	2 (29%)	0 (0%)
Suicide Attempt	2 (29%)	0 (0%)
Syncope	1 (14%)	0 (0%)
Tonsillitis	1 (14%)	0 (0%)

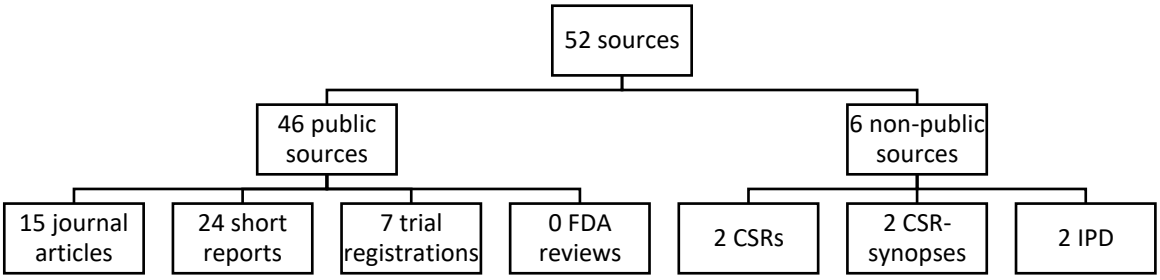
Appendix Figure 2-1. Number of sources of each type

Appendix Figure 2-1 Legend: FDA=Food and Drug Administration; CSR=clinical study report; IPD=individual participant data.

Panel 2-1a. Gabapentin for neuropathic pain



Panel 2-1b. Quetiapine for bipolar depression



Chapter 3. Aim 2

Reporting of systematically collected adverse events in public and non-public sources about randomized clinical trials: Quetiapine for bipolar disorder as a case example

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Abstract

Background: Informed healthcare decisions should be based on evidence about both the effectiveness and adverse events (AEs) of interventions. AEs that are suspected of being related to an intervention may be collected "systematically" (e.g., through a specific interview question about whether the AE has occurred or administration of a laboratory test). The objectives of this study were to describe, across eligible randomized controlled trials (RCTs), the collection and reporting of AEs collected systematically ("systematic AEs") and to compare systematic AE reporting in "public" (e.g., journal articles, conference abstracts) and "non-public" (e.g., clinical study reports [CSRs], individual patient data [IPD]) sources.

Methods and Findings: We performed a cross sectional analysis of the Multiple Data Sources (MUDS) study data. In the MUDS study, we examined consistency across the various sources of information about RCTs of both gabapentin for neuropathic pain and quetiapine for bipolar depression. Because the gabapentin RCTs did not report any systematic AEs, this analysis included only quetiapine RCTs. We identified public and non-public sources available by January 26, 2015. We extracted data from each source and compared reporting about systematic AEs in each of the following six pre-specified outcome domains: cardiovascular effects, cholesterol, endocrine effects, extrapyramidal symptoms, mania, and weight. Each systematic AE "outcome" included five elements: outcome domain, specific measurement, specific metric, method of aggregation, and time-point. Outcomes were considered "defined" if all five elements were reported. We

compared what was reported for each outcome in public and non-public sources. We assessed whether reported results were “meta-analyzable” (i.e., one could calculate between-group effect estimates) and compared public and non-public sources. We compared the number of unique defined outcomes (i.e., an outcome was counted once, regardless of how many times outcome was named) in public and non-public sources.

We identified seven eligible trials reported in 51 sources (including one IPD). Including both public and non-public sources, 1/6 pre-specified AE outcome domains (mania) was reported for all seven trials, and 3/7 trials reported meta-analyzable results related to mania. Public sources reported less complete information about results: about half (90/159; 57%) of all results reported in public sources were both associated with defined outcomes and meta-analyzable, compared with nearly all (610/636; 96%) results reported in non-public sources. Public sources also reported fewer unique outcomes compared with non-public sources (38 vs. 113).

Conclusions and Relevance: To effectively compare different potential interventions, systematic AE outcomes must be consistently collected and reported across trials. Systematic AEs are often reported only in non-public sources, where more meta-analyzable data are also found. All trial information should be available to the public so that the entire body of evidence is considered as the basis for treatment decisions and guideline creation. This is particularly true for systematic AEs, which represent important concerns for patients and are selected for systematic collection because of their suspected association with an intervention.

Introduction

When choosing a health intervention, patients and clinicians need accurate and complete information about potential benefits and adverse events (AEs) to inform their decision. Outcomes that assess potential benefits are typically collected systematically by using, for example, closed-ended interview questions or laboratory tests, as part of randomized controlled trials (RCTs). In contrast, AEs can be collected using both systematic and non-systematic methods. Non-systematic AEs are either unsolicited by investigators or collected using broad, open-ended questions such as "have you noticed any symptoms since your last examination?" Because systematic methods of data collection are the same for every participant within a trial, investigators may use systematic methods when they suspect that a particular AE is related to an intervention. The understanding of which AEs may be related to an intervention often evolves as more data accumulate, potentially informing whether additional AEs should be collected systematically in subsequent studies. More often, however, AEs are collected using non-systematic methods, and some trials do not collect any AEs systematically (4).

The "systematic" and "non-systematic" terminology to describe different methods of AE data collection was established by the Final Rule, which establishes and clarifies federal reporting requirements for ClinicalTrials.gov (5, 6). Although the Food and Drug Administration (FDA) makes a similar distinction between methods of AE data collection, it uses different terminology (20). The FDA states that "[p]otential problems that may be suspected because of preclinical data or because of effects of related drugs

should be targeted for evaluation" (13); however, we were unable to find any evidence that the FDA has policies *requiring* that any or specific AEs be collected systematically (13, 19, 20). Therefore, even when investigators conducting trials elect to collect certain AEs systematically, there may not be a core set of specific AE outcomes collected in all trials about particular conditions or interventions. The result of this individualistic approach is that different trials for the same indication and intervention may collect data about different AE outcomes, even when some data collection is systematic within the individual RCT.

All outcomes, including effectiveness outcomes and AEs, can be *defined* using a framework that includes five elements, although this framework is not always applied: (1) domain (e.g., mania); (2) specific measurement (e.g., Young Mania Rating Scale); (3) metric (e.g., a participant's change in Young Mania Rating Scale from baseline); (4) method of data aggregation for analysis (e.g., mean Young Mania Rating Scale score, proportion of participants reaching a particular threshold); and (5) time-point at which the outcome was assessed (11, 12). Because systematic AEs are collected using pre-specified questions and methods, this framework can be used; non-systematic AEs are collected using open-ended questions without a specific measurement tool, however, and therefore this framework is not applicable.

Results of RCTs may be made available in a variety of sources, including both public (e.g., journal articles) and non-public (e.g., clinical study reports [CSRs]) sources. Evidence shows that public sources may contain less information about AEs than non-

public sources about the same trial (46, 48, 50, 69, 220), and different public sources may contain different information (38, 39, 88, 89, 220). Access to partial information, such as that contained in public sources alone, may impact the perceived balance of potential benefits and AEs if information is differentially reported in public and non-public sources.

In the current study, our objectives were to describe collection and reporting of systematic AEs identified in RCTs of quetiapine for bipolar depression across multiple sources of data, and to compare reporting of AEs in public and non-public sources. Our investigation of non-systematic AEs is reported elsewhere (220).

Methods

This analysis is a sub-study of the Multiple Data Sources (MUDS) study, a cross-sectional study that compares reporting of RCTs in public and non-public sources. The protocol (81) and protocol amendments (90) provide additional details about the MUDS study methods. We have also reported additional details in Appendix 3-1 (220).

Eligible trials and sources

Briefly, eligible studies were parallel RCTs that compared either gabapentin for neuropathic pain in adults or quetiapine for bipolar depression in adults with placebo; participants and providers were masked (220). In the current study, we report only on the quetiapine RCTs, because neither the public or non-public sources for gabapentin trials reported any systematic AEs. The six gabapentin CSRs did, however, report that physical exams were conducted at the end of the RCTs. We use “public sources” to refer

to journal articles, short reports (i.e., conference abstracts, commentaries, posters), trial registrations and associated results, and medical and statistical reviews created by the FDA. We use "non-public sources" to refer to CSRs, CSR-synopses, and IPD, because they are usually not available to the public. We searched for public and non-public sources and requested additional non-public sources from the company that manufactures quetiapine (see Appendix 3-1 and protocol (81) for additional details).

Data extraction

We classified AEs as systematic or non-systematic (5, 6). We pre-specified that we would classify AEs as systematic when they were reported as being obtained using specific measurement tools such as questionnaires, checklists, laboratory tests, and clinical examinations that were done on every patient. All other AEs were classified as non-systematic (220). Our analysis in this study focused exclusively on systematic AEs.

Two investigators independently extracted data about AEs using the open access Systematic Review Data Repository (SRDR; http://srdr.ahrq.gov/) and resolved any differences by discussion. For systematic AEs, we extracted information from each source about the five elements of each outcome for the time-point closest to 8 weeks (11, 12). We extracted all outcomes and results within each of the following pre-specified systematic AE outcome domains: cardiovascular effects, cholesterol, endocrine effects, extrapyramidal symptoms, mania, and weight.

Analysis of IPD

When IPD databases were not available, we used ABBYY FineReader (91) to reconstruct databases using tables of IPD (in PDF format) in the appendices of CSRs. For continuous outcomes in the available IPD, we calculated the mean change from baseline for the time-point closest to eight weeks for each specific measurement. For dichotomous outcomes, we calculated the proportion of participants who experienced each AE outcome. We calculated between group effects for both continuous (mean difference between groups) and dichotomous (risk difference) outcomes. We replicated the methods for handling missing data used in the original trials. We performed all analyses in Stata 14 (92).

Outcome domains collected and reported in each trial

Because of the detailed methods reported in CSRs (see Table 3-1) (42), we considered CSRs the reference for which systematic AEs were collected during the trial. For trials with available CSRs, we determined whether each trial collected each of the six pre-specified AE outcome domains. For all trials, we determined whether any public or non-public source reported any of the six pre-specified AE outcome domains.

Completeness of outcome reporting in different types of sources

We described results as “meta-analyzable” when we could calculate between group effects (e.g., mean difference between groups, risk difference) (63).We assessed whether each reported result was associated with a “defined” outcome (i.e., all five elements were reported). We calculated the proportion of all results that were meta-

analyzable and associated with defined outcomes. We then compared these proportions for public and non-public sources. This analysis includes results associated with both unique outcomes (i.e., defined outcomes counted only once regardless of how many times they appeared, Table 3-1) and non-unique outcomes (i.e., defined and undefined outcomes counted each time they appear, Table 3-1). Results could be meta-analyzable, but not associated with a defined outcome. For example, a source might include both a mean and standard deviation for participants' scores on a particular questionnaire, but not report the time-point.

Comparison of unique outcomes across sources

We counted the number of unique AE outcomes and the number of unique outcomes with meta-analyzable results. We then compared public and non-public sources, as well as specific sources (e.g., journal articles, CSRs). We calculated the number of unique AE outcomes both across all eligible trials and for each trial separately.

Meta-analyzable results reported in public and non-public sources

For each trial, we compared the effect estimates (i.e., comparing quetiapine with placebo) in public and non-public sources. For continuous outcomes, we calculated a standardized mean difference (SMD). For dichotomous outcome, we calculated a risk difference. We plotted the SMDs and risk differences reported in public and non-public sources.

Results

Search results

We identified seven eligible trials of quetiapine for bipolar depression reported in 51 sources, including 46 (90%) public sources and one IPD. Most public sources were short reports (24/46, 52%) and journal articles (15/46, 33%). We obtained CSRs for two trials and CSR-synopses for two additional trials (Appendix Figure 3-1).

We requested additional non-public sources from the company sponsoring all seven eligible quetiapine trials; our request was denied, however (93). One of the two CSRs had extensive appendices; from other information in the CSR, we believe that the IPD tables in this CSR were complete. The IPD tables in this CSR included data about systematic AEs. The second CSR had fewer appendices available and did not contain any IPD tables that included any systematic AEs. Because we did not obtain any IPD related to systematic AEs for this trial, we counted only the first trial as having IPD in this analysis.

Summary data in CSRs matched reanalyzed IPD

We had IPD related to systematic AEs for only one trial (Calabrese 2004). The IPD contained information about all of the outcome domains and specific measurements we found in the corresponding CSR (i.e., all questionnaires, laboratory tests, and vital signs for which we found aggregate data in the CSR were available in the IPD). When we analyzed the IPD, we found results that were similar (within rounding error) or identical to the aggregate data reported in the corresponding CSR.

Outcome domains were not collected and reported consistently across trials

Although some AEs were collected systematically, eligible trials did not collect and report the same AEs. From the CSRs, we were able to determine which outcomes were collected systematically in two trials. For the remaining five trials without CSRs, we were unable to differentiate between outcomes that were not collected and outcomes that were collected but not reported. Not all of our pre-specified outcome domains were collected in all trials: for example, the two trials for which we have CSRs did not collect any systematic AEs in the endocrine effects domain, but two other trials reported outcomes within this domain.

Only one pre-specified AE outcome domain, "mania," was reported for all seven eligible trials, although the outcome data were meta-analyzable in only 3/7 trials (Table 3-2). The outcome domains with the largest number of trials that could be included in a meta-analysis were weight and cholesterol: in both cases 5/7 trials reported at least one meta-analyzable result in at least one source, public or non-public. For cholesterol, however, meta-analyzable results were reported in only non-public sources for two of these trials (Table 3-2).

Public sources reported less information than non-public sources about outcomes and results

Results in public sources were less likely to be meta-analyzable and associated with defined outcomes than results in non-public sources. More than half (90/159; 57%) of results reported in public sources were both meta-analyzable and associated with

defined outcomes, compared with nearly all (310/636; 96%) results reported in non-public sources (Table 3-3). Most of the results (138/159; 87%) reported in public sources were found in journal articles. Journal articles were the only public source to include meta-analyzable results associated with defined outcomes.

Although we had public sources for 7/7 trials and non-public sources for 4/7 trials, public sources reported fewer unique outcomes than non-public sources (38 vs. 113, respectively). Public sources reported meta-analyzable results for 28/38 (74%) unique outcomes, while non-public sources reported meta-analyzable results for 112/113 (99%) unique outcomes. We found that different kinds of public sources (e.g., journal articles, trial registrations) reported different numbers of unique outcomes (Appendix Table 3-2).

Meta-analyzable results reported in public and non-public sources for two trials

Two trials included meta-analyzable results in both public and non-public sources (Calabrese 2004 and Thase 2006). Journal articles were the only public sources with meta-analyzable results (Figure 3-1). CSRs for both trials reported meta-analyzable results; we also had meta-analyzable results in IPD for Calabrese 2004. The non-public sources about both trials reported many different meta-analyzable results about each of the five outcome domains they assessed (Figure 3-1). Many results were related to each outcome domain because of variations in the specific measurement, metric, and method of aggregation (note that we extracted data for only one time-point). For example, both trials measured the outcome domain “extrapyramidal symptoms” using

two different questionnaires: the Barnes Akathisia Rating Scale and the Simpson-Angus Scale.

For Calabrese 2004 and Thase 2006, we found meta-analyzable results in both public and non-public sources for three outcome domains: mania, weight, and extrapyramidal symptoms (Figure 3-1). Although results were often unreported in public sources, they appeared to agree with results in non-public sources when they were reported (Figure 3-1).

Discussion

Although certain AEs were systematically collected, not all trials systematically collected and reported the same AEs. We were able to determine which outcome domains were collected using CSRs for two trials. For the five trials for which we did not have CSRs or IPD, we were unable to determine which outcome domains were not collected and which outcome domains were collected but not reported.

When trials do not assess the same AEs, as occurred in this analysis, healthcare decisions may be based on some of the available trials. Core outcome sets ("an agreed minimum set of outcomes" (23, 24)) could improve consistency across trials by identifying systematic AEs that should be assessed in all trials of a condition or intervention. Typically, core outcome sets are associated with a particular disease or condition (24), but this may be inappropriate when assessing AEs. Different types of interventions (e.g., psychotherapy vs. pharmaceutical interventions) may cause different AEs, and a single intervention can be used to treat several conditions (e.g., quetiapine is

used to treat bipolar depression and schizophrenia). Therefore, it may be more appropriate to have a core outcome set of systematic AEs for an intervention or group of interventions (e.g., a drug class), rather than a condition.

To improve estimates of the probability that patients will experience AEs, and to permit comparisons across trials, investigators might collect anticipated AEs systematically. It can be difficult to anticipate which AEs will occur in the first clinical trials of a drug or class of drugs, so investigators often collect information about many AEs non-systematically. In later trials, investigators could use evidence from early trials to anticipate which AEs might occur. Because evidence accumulates over time, core outcome sets may need to be periodically updated to incorporate the latest evidence.

Using systematic and non-systematic methods to collect data about AEs can lead to different results (15, 18, 221). For example, patients may be more likely to report an AE when systematic methods are used (15). Thus, we question whether it is appropriate to compare the relative safety of different interventions when trials used different methods to assess AEs.

Although most AEs are collected non-systematically, it may be more valid and reliable to use systematic methods to collect AEs. Validity and reliability are critical indicators of measurement quality (222). There are well-established methods for assessing the validity and reliability of instruments, such as those used in systematic data collection (222-224). Because non-systematic methods do not utilize instruments, there are no currently available methods for assessing the validity or reliability of non-

systematic AEs. Using valid and reliable instruments to collect AEs *systematically* will improve the quality of research.

The five elements of an outcome (11, 12) should be pre-specified for systematic AEs. As we and others have shown (63), variations in these elements can lead to a very large number of outcomes and associated results within a single trial and across multiple trials. If the five elements and the methods of analysis are not pre-specified, trialists and systematic reviewers may "cherry-pick" outcomes based on their results (63).

Both results and details about collection methods should be made public so that decision-makers can take all evidence about benefits and AEs into account. The Consolidated Standards of Reporting Trials (CONSORT) extension for harms provides specific reporting standards (36). We did not find that this information was typically available in public sources or CSR-synopses. From our findings we surmise that ClinicalTrials.gov may not be a good source of information about trials conducted before registration and results policies were in place, although we only have evidence about one intervention. We were unable to identify any FDA reviews of quetiapine for bipolar depression, so further research is needed to determine if FDA reviews contain more information about systematic AEs than other public sources. Increased accessibility of FDA reviews is important; they are currently unavailable to the public in some cases. If data are made available in the form of IPD, meta-data (e.g., descriptions of variables and

their content) and methodological information (e.g., how AEs were collected) should also be shared to increase transparency.

Non-public sources are often unavailable and, as with the other intervention we examined in MUDS (gabapentin for neuropathic pain), AEs may not be collected systematically. Although our analysis focused on a single intervention, our findings are consistent with other studies about AE collection and reporting. This suggests that our recommendations (Box 3-1) may be applicable in a broader context. For trials that are being conducted and published now, adherence to the existing guidelines for reporting AEs (36) could improve the quality and amount of AE data reported. For trials that have already been published, however, further steps should be taken. Our findings here are consistent with those that suggest access to non-public sources may be critical to understanding the potential benefits and AEs of an intervention (45, 63, 69, 90, 225).

Table 3-1. Glossary of Terms

<table>
<tr><th>Term</th><th>Definition/Example</th></tr>
<tr><td colspan="2">Adverse events</td></tr>
<tr><td>Non-systematic adverse events (Final Rule)[1]</td><td>Adverse events that are collected using open-ended questions or are spontaneously reported by participants. For example, adverse events collected by asking participants questions like “Have you noticed any symptoms since your last examination?”</td></tr>
<tr><td>Systematic adverse events (Final Rule)[1]</td><td>Adverse events that are collected in the same manner for each participant using methods related to specific adverse events. For example, adverse events collected using validated questionnaires, checklists, laboratory measurements, or vital signs.</td></tr>
<tr><td colspan="2">Sources</td></tr>
<tr><td>Public sources[1]</td><td>In this study, public sources include journal articles, conference abstracts, commentaries, posters, trial registrations and associated results, and medical and statistical reviews created by the Food and Drug Administration.</td></tr>
<tr><td>Non-public sources[1]</td><td>In this study, non-public sources include individual patient data, clinical study reports, and clinical study report-synopses.</td></tr>
<tr><td>Clinical study report (CSR)[1]</td><td>A comprehensive document created by a pharmaceutical company detailing the design, methods, analyses, and results of a single study for submission to regulatory agencies. The clinical study reports we examined ranged in length from 1315 to 8027 pages. Appendices contain tables of individual participant data, also called “patient data listings.”</td></tr>
<tr><td>Clinical study report synopsis (CSR-synopsis)[1]</td><td>An internal company document that summarizes the information contained in clinical study reports. Clinical study report-synopses are much shorter than clinical study reports; the two clinical study report-synopses we examined were each 13 pages in length.</td></tr>
<tr><td>Individual participant data (IPD)[1]</td><td>Each record lists data separately for each participant. In the below example, the data include a participant identifier (“PTNO”), text describing the adverse event (“AETX”), whether the AE was classified as serious (“AESER”), the day of the study that the event occurred (“SDAESTDY”), and a standardized code for grouping AEs that are clinically equivalent (“AE”; e.g., “giddy” and “giddiness” have the same code). There is a separate record for each participant and each different AE. For example, participant 167 experienced three different AEs (tiredness, headache, and septic foot).
<table>
<tr><th>PTNO</th><th>AETX</th><th>AESER</th><th>SDAESTDY</th></tr>
<tr><td>163</td><td>DROWSINESS</td><td>0</td><td>2</td></tr>
<tr><td>164</td><td>GIDDY</td><td>0</td><td>28</td></tr>
<tr><td>166</td><td>GIDDINESS</td><td>0</td><td>2</td></tr>
<tr><td>167</td><td>TIREDNESS</td><td>0</td><td>11</td></tr>
<tr><td>167</td><td>HEADACHE</td><td>0</td><td>16</td></tr>
<tr><td>167</td><td>SEPTIC FOOT</td><td>0</td><td>22</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Outcomes and results</td></tr>
</table>

Outcome[2]	An event in a person, used to assess a treatment's effect (226). May be defined using all elements or not defined.
Defined outcome[2]	Includes all five elements of an outcome: (1) outcome domain, (2) specific measurement, (3) specific metric, (4) method of aggregation, and (5) time-point. For example "proportion of participants with 50% change from baseline to 8 weeks on the Young Mania Rating Scale total score."
Not defined outcome[2]	Includes the name of an outcome domain but does not include one or more of the other 4 elements; for example, "symptoms of mania at 8 weeks."
Result[2]	A numerical contrast between a treatment and comparison group (e.g., relative risk, mean difference).
Meta-analyzable result[2]	A result for which sufficient information was provided to calculate the between group effect (e.g., a point estimate and a measure of precision).
Unique outcome[2]	Defined outcome which is counted only once, regardless of how many times it appeared in all sources.
Non-unique outcome[2]	Outcome counted each time it appears in sources. Note that if the same outcome is reported more than once in the same source (e.g., in text and in a table), it is counted just once for that source.

[1] Item identical to an item used in our research on non-systematic AEs (220).

[2] Item adapted from and used consistently with our research on effectiveness outcomes (63).

Table 3-2. Trials reporting each adverse event outcome domain in public sources, overall and with meta-analyzable results

	Pre-specified AE outcome domains					
	Cardiovascular effects	**Cholesterol**	**Endocrine effects**	**Extrapyramidal symptoms**	**Mania**	**Weight**
Trial reporting AE outcome domain in public sources						
Calabrese 2004				✓	✓	✓
Gao 2014				*	✓	
Li 2014					*	
McElroy 2010		✓	✓	✓	*	✓
Suppes 2010		✓		*	*	✓
Thase 2006				✓	✓	✓
Young 2008		✓	✓	*	*	✓

Legend:

* At least one public source for that trial reported at least one result within the outcome domain.

✓At least one public source for that trial reported at least one meta-analyzable result within the outcome domain.

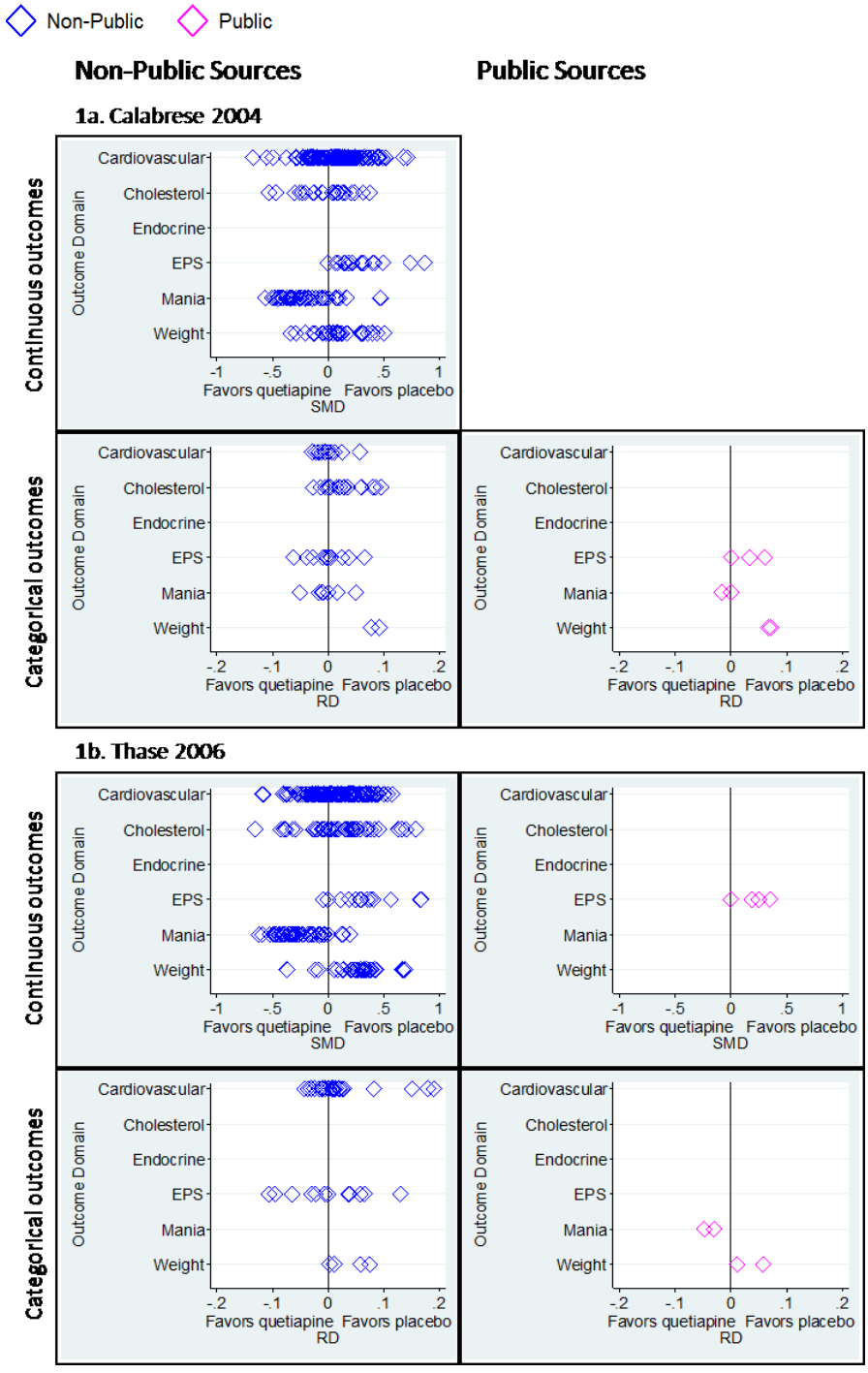
Table 3-3. Proportion of results that are meta-analyzable and associated with defined adverse event outcomes, by source

Meta-analyzable result?	**Public Sources (n=159)** Defined outcome?		**Non-Public Sources (n=636)** Defined outcome?	
	Defined	Not defined	Defined	Not defined
Meta-analyzable	90 (57%)	2 (1%)	610 (96%)	20 (3%)
Not meta-analyzable	35 (22%)	32 (20%)	2 (0.3%)	4 (0.6%)

Meta-analyzable result?	**Journal Articles (n=138)** Defined outcome?		**Other Public Sources (n=21)** Defined outcome?	
	Defined	Not defined	Defined	Not defined
Meta-analyzable	90 (65%)	2 (1%)	0 (0%)	0 (0%)
Not meta-analyzable	34 (25%)	12 (9%)	1 (5%)	20 (95%)

Figure 3-1. Systematic adverse event outcomes in public and non-public sources for two trials

Legend: This figure includes the two trials that reported meta-analyzable results in both public and non-public sources. While non-public sources about each trial included hundreds of results, public sources included fewer than 10 results and omitted outcome domains included in non-public sources. **SMD**=standardized mean difference (used for continuous outcomes); **RD**=risk difference (used for dichotomous outcomes); **EPS**=Extrapyramidal Symptoms.



Box 3-1

Recommendations for adverse event collection and reporting

1. Describe collection methods for each adverse event (AE) in the trial protocol and provide case report forms;
2. Develop, regularly update, and use a core outcome set for AEs for interventions or groups of interventions (e.g., drug class);
3. Incorporate both potential AEs and potential benefits into the design and reporting of a trial;
4. Report defined outcomes and meta-analyzable results for AEs;
5. Collect data on known AEs systematically;
6. Use preclinical studies and trials of other drugs in the same class to inform systematic AE collection;
7. Make results of all AEs, collection and analysis methods, and full outcome definitions, available to the public; one potential mechanism is for the FDA to release the information that is submitted to them.

Appendix 3-1. Detailed methods

Identifying sources about eligible trials

We searched both the International Clinical Trials Registry Platform Search Portal (ICTRP) and ClinicalTrials.gov for trial registrations and associated results related to gabapentin or quetiapine on October 10, 2014. We searched PubMed, Embase, Lilacs, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) for gabapentin and quetiapine sources, as well as PsycInfo for quetiapine; we completed our searches March 2, 2015 (gabapentin) and January 26, 2015 (quetiapine), without any language restrictions. We identified medical and statistical reviews of gabapentin as well as quetiapine available on the FDA website (26). We also searched certain conference proceedings and years for gabapentin trials (see protocol (81)). We searched online (http://psychrights.org/) for typically non-public sources about quetiapine for bipolar depression. We requested non-public sources in the form of internal company documents from the manufacturers of gabapentin and quetiapine (Pfizer and AstraZeneca, respectively). We identified the trial(s) reported in each source and grouped sources by the trial(s) described.

Appendix Table 3-1. Systematic adverse event outcome domains and measurements identified

Adverse Event Outcome Domains	Adverse Event Outcome Specific Measurements
Cardiovascular effects	Pulse Systolic blood pressure Diastolic blood pressure QT interval QTc interval
Cholesterol	Triglycerides Total cholesterol HDL cholesterol LDL cholesterol
Endocrine effects	Serum prolactin
Extrapyramidal symptoms	Barnes Akathisia Rating Scale (BARS) Simpson-Angus Scale (SAS)
Mania	Young Mania Rating Scale (YMRS)
Weight	Weight Body mass index (BMI)

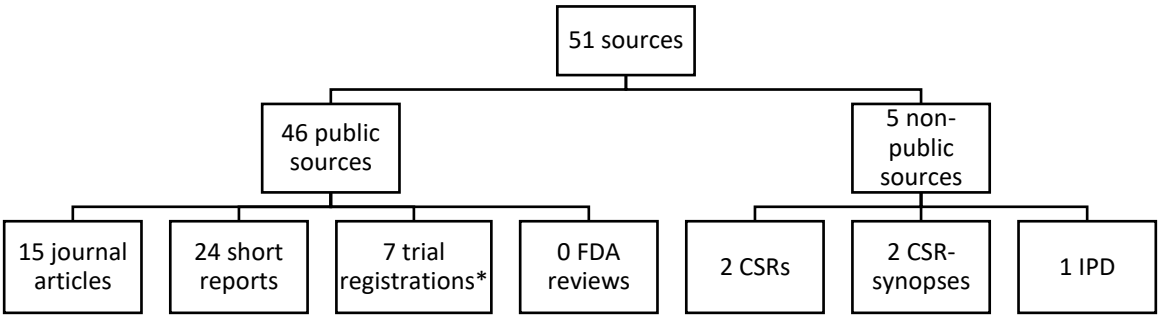
Appendix Table 3-2. Number of unique, defined, systematic adverse event outcomes in public and non-public sources, by trial

	Public Sources												Non-Public Sources						All Sources	
	Journal Articles				Short Reports				ClinicalTrials.gov		All Public		CSR		CSR-S		All Non-Public			
	1 Trial		>1 Trial		Abstracts		Other													
Trial Identifier	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**	**All**	**MA**
Calabrese 2004 (170-195)	7	4	0	0	0	0	0	0	0	0	7	4	98	98	NA	NA	98	98	99	99
Gao 2014 (196, 197)	3	1	NA	NA	NA	NA	NA	NA	0	0	3	1	NA	NA	NA	NA	NA	NA	3	1
Li 2014 (198, 199)	NA	NA	NA	NA	0	0	NA	NA	1	0	1	0	NA	NA	NA	NA	NA	NA	1	0
McElroy 2010 (170-176, 200-204)	22	20	0	0	0	0	0	0	0	0	22	20	NA	NA	1	0	1	0	23	20
Suppes 2010 (205-207)	15	7	NA	NA	0	0	NA	NA	0	0	15	7	NA	NA	NA	NA	NA	NA	15	7
Thase 2006 (170-180, 208-213)	5	4	0	0	0	0	0	0	0	0	5	4	106	106	NA	NA	106	106	107	107
Young 2008 (170-176, 200, 214-219)	16	12	0	0	0	0	0	0	0	0	16	12	NA	NA	0	0	0	0	16	12
Total	**38**	**28**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**38**	**28**	**1**	**0**	**112**	**112**	**113**	**112**	**127**	**124**

MA=meta-analyzable; NA=not applicable because we did not identify any sources of this type; CSR=clinical study report; CSR-S=CSR-synopsis. Note that individual patient data (IPD) were not included in this table because some elements of a defined outcome are not applicable to IPD; for example, IPD are not aggregated, so there is no method of aggregation.

Appendix Figure 3-1. Number of sources of each type

FDA=Food and Drug Administration; CSR=clinical study report; IPD=individual participant data (note that IPD were included in only a subset of our analyses); *All trial registrations were found on ClinicalTrials.gov.



Chapter 4. Aim 3

Opportunities for selective reporting of non-systematic adverse events in randomized controlled trials

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Abstract

Background: In randomized controlled trials (RCTs), most adverse events (AEs) are collected non-systematically (e.g., experience of the AE was not solicited). Although RCTs may be reported in multiple sources, AEs may not always be reported. The objectives of this study were to (1) compare "selection criteria" (i.e., reported methods for selecting which AEs to report from an RCT) for reporting non-systematic AEs; (2) determine how different selection criteria could affect AE reporting; and (3) assess how different selection criteria could impact the results of meta-analyses of AEs.

Methods: We compared data sources (e.g., journal articles, clinical study reports) about RCTs examining either gabapentin for neuropathic pain or quetiapine for bipolar depression (data available by March 2, 2015 and January 26, 2015, respectively). We extracted and compared information about selection criteria for reporting non-systematic AEs and assessed how the choice of selection criteria impacted AEs reported. We simulated meta-analyses of AEs in small and large RCTs, assuming different "true" proportions of patients experiencing the AE in each trial and assessed whether the AE would have been reported, based on the numerical threshold (e.g., ≥5%) for reporting.

Results: We identified 21 gabapentin trials and 7 quetiapine trials. Although the majority of sources included non-systematic AEs, AEs were chosen for reporting based on selection criteria and represented a subset of the AEs that occurred. We found no evidence in study protocols that selection criteria were pre-specified. The choice of selection criteria for reporting had a meaningful impact on the number of different AEs

reported for all trials. For example, while all trials we observed would report many AEs if the selection criterion was “occurred in ≥1% of any intervention group,” trials would report few AEs if the selection criterion was “occurred in ≥10% of all participants.” Our simulations showed that the choice of different selection criteria could result in either (1) meta-analyses of non-systematic AEs incorrectly indicating no harmful effect of the intervention or (2) no possible meta-analyses because of unreported AEs.

Conclusions: By not pre-specifying selection criteria for reporting, trialists can “cherry-pick” which AEs to report. Data about all non-systematic AEs identified in trials must be reported to all stakeholders to facilitate evidence-based healthcare decisions.

Introduction

The effectiveness and safety of health interventions may be considered best assessed through randomized controlled trials (RCTs) (227), and regulatory approval is typically based on the results of RCTs (4). Effectiveness outcomes are typically used to estimate sample size and power of a trial to detect a true difference between treatments (4), but RCTs are not typically powered to detect differences the occurrence of adverse events (AEs) in the study population (see Table 4-1 for a glossary of terms used) (72). Because regulatory agencies require the collection of non-systematic AEs (i.e., the occurrence of an AE is ascertained either from unsolicited reporting by participants or from general questions such as "have you noticed any changes since your last visit?" (5, 6)) (4, 21), our understanding is that information about the experience of most AEs is collected using non-systematic methods. AEs can also be collected systematically, using, for example, questionnaires, checklists, and laboratory tests (5, 6). Unlike non-systematic AEs, systematic AEs are typically pre-specified during trial design (5).

Systematic reviews and meta-analyses provide the opportunity to combine AE data from multiple RCTs, which, because AEs usually occur infrequently, may allow the detection of between-group differences not identified in individual RCTs. Although more resources are becoming available through data sharing initiatives (228, 229), systematic reviews and meta-analyses of AEs typically rely on AE data that have been publicly reported (77).

Existing evidence shows that the results of RCTs may not be made publicly available (56, 58), and that even when RCTs are published, reporting may be incomplete (58-63, 71, 90, 220, 230). Outcome reporting bias, defined as the "selective reporting of some outcomes but not others, depending on the nature and direction of the results" (64), may affect the findings of systematic reviews and meta-analyses that are based on the publicly reported results of these RCTs (65-68). The presence of outcome reporting bias has been well-established for effectiveness outcomes in RCTs (58-63).

Although we know that multiple sources (e.g., journal articles, conference abstracts) describing the same RCT sometimes report different non-systematic AEs and that many non-systematic AEs are unreported in public sources (38, 39, 46, 48, 50, 69, 88, 89, 220), there is little evidence about AE selection criteria (i.e., reported methods for choosing which AEs to include in a source, see Table 4-1). Non-systematic AEs that occur during a particular trial might meet some selection criteria, but not others. For example, an AE that occurred in 4% of all participants would be reported if selection criteria specified that AEs would be reported if they occurred in ≥2% of all participants, but not if selection criteria specified ≥5% of all participants.

ClinicalTrials.gov, an important data source about trials, has different reporting requirements for non-systematic and systematic AEs. The Final Rule, which describes requirements for reporting RCTs in ClinicalTrials.gov, states that non-systematic AEs that occur in ≥5% of any intervention group should be entered in ClinicalTrials.gov (5). Because systematic AEs are pre-specified, the Final Rule states that the results of all systematic AEs should be reported (5). The Final Rule also requires reporting of all

"serious" AEs, defined by the Food and Drug Administration (FDA) as "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (19). We have shown previously that not all serious AEs are reported (220). Because guidelines are clear that *all* serious AEs and systematic AEs should be reported, while only a subset of non-systematic AEs should be reported, this analysis focused exclusively on non-systematic AEs.

The objectives of this study were to (1) compare selection criteria for reporting non-systematic AEs; (2) determine how different selection criteria could affect AE reporting; and (3) assess how different selection criteria could impact the results of meta-analyses of AEs for two case studies, RCTs examining gabapentin for neuropathic pain or quetiapine for bipolar depression.

Methods

This analysis is a sub-study of the Multiple Data Sources (MUDS) study, a cross-sectional study that compares reporting of RCTs in public and non-public sources. The protocol (81) and protocol amendments (90) provide additional details about the MUDS study methods, including search strategies. We have also reported additional details in Appendix 4-1 (220).

Eligible trials and sources

Briefly, we defined eligible studies as parallel RCTs, in which both participants and providers were masked, that compared either gabapentin for neuropathic pain in adults or quetiapine for bipolar depression in adults compared to placebo. We use "public sources" to refer to journal articles, short reports (i.e., conference abstracts, commentaries, posters), trial registrations and associated results, and medical and statistical reviews created by the FDA. We use "non-public sources" to refer to clinical study reports (CSRs), CSR-Synopses, and individual participant data (IPD), which are usually not available to the public. We searched for public and non-public sources and requested additional non-public sources from the companies that manufacture gabapentin and quetiapine (see Appendix 1 and protocol (81) for additional details) (220). In this analysis, we focused on the *reporting* of trials; because IPD do not contain reported methods, we excluded IPD from this analysis.

According to guidelines created by the International Conference on Harmonisation, CSRs should contain summary data about *all* AEs in clinical trials (42). We therefore considered CSRs the reference standard for determining which AEs occurred during a trial.

Data extraction

Two investigators independently extracted data about non-systematic AEs using the open access Systematic Review Data Repository (SRDR; http://srdr.ahrq.gov/) and resolved any differences by discussion. We extracted the name of the non-systematic AE (e.g., "dizziness") and the associated results (e.g., number or proportion of participants

experiencing an AE), if available. We extracted information about AEs even when results were not reported; for example, if a source reported that "the most common AEs were dizziness and headache," we extracted dizziness and headache as reported AEs) (220). We also extracted all reported methods about how AEs were selected for inclusion in the source ("selection criteria").

Comparing AE selection criteria for reporting across sources and trials

We assessed which sources reported non-systematic AEs, and when they were reported, we assessed AE selection criteria, if any. We described the different selection criteria reported and assessed whether multiple sources about the same trial reported using the same selection criteria. When possible, we described selection criteria using four components:

- **Numerical threshold**: a cutoff for reporting the number or proportion of participants who reported experiencing a specific AE (e.g., ≥5% of participants).
- **Participant group**: specification of which group(s) must experience a particular AE to be reported (e.g., participants in a specific intervention group, all participants in the trial).
- **Difference in frequency threshold**: a cutoff for reporting a difference in the number or proportion of participants experiencing a specific AE, comparing one intervention relative with another (e.g., more frequent in one intervention compared to another, twice as frequent in the active intervention group compared with the placebo group).

- **Statistical significance threshold**: a cutoff for reporting a statistically significant difference in the number or proportion of a specific AE in participants receiving one intervention relative to another (i.e., there is a statistically significant difference in the frequency of AEs between the active intervention group and the placebo group).

We described each reported component for all selection criteria. Below we show some examples of selection criteria, with each component identified by color:

Numerical threshold for reporting **Difference in frequency threshold**

Participant group **Statistical significance threshold**

Selection criteria example 1:

Adverse events are reported if they occur in ≥5% of participants in any intervention group.

Selection criteria example 2:

Adverse events are reported if they occur in ≥2% of participants receiving gabapentin and if they occur at least twice as frequently in participants receiving gabapentin, compared with participants receiving placebo.

Selection criteria example 3:

Adverse events are reported if they occur in ≥1% of all participants and if they occur statistically significantly more frequently in participants receiving quetiapine, compared with participants receiving placebo.

We compared which non-systematic AEs were reported in multiple sources about the same trial(s); we did not compare AEs reported in sources that did not report any selection criteria. We also compared information reported in CSRs, which included data about all observed AEs and did not utilize selection criteria (42), with the non-systematic AEs in sources that reported selection criteria. For example, if a source about a trial reported that it included all AEs occurring in ≥5% of all participants, we used the CSR for the same trial to identify which AEs met this selection criterion. We then compared our findings from the CSR with the AEs reported in other sources.

Applying AE selection criteria to data in individual trials

To assess how using different selection criteria affects which and how many non-systematic AEs would be reported, we applied multiple selection criteria to the data in CSRs, when CSRs were available (six gabapentin trials and two quetiapine trials). We used the selection criteria reported in sources about eligible studies as a basis for the selection criteria we applied. We combined each numerical threshold for reporting we identified with each participant group, difference in frequency threshold, and statistical significance threshold we identified. We then determined which non-systematic AEs would meet each of the selection criteria for each trial. For example, we examined the reported data for each different AE in the CSR and assessed whether each reported AE met the selection criterion "occurring in ≥5% of participants in any intervention group, with no additional requirements for difference in frequency or statistical significance." We then calculated and compared the total number of different AEs that met each of the selection criteria within each trial.

Simulations of meta-analyses of RCTs with different AE selection criteria for reporting

A simulation uses computer-generated data to model events in cases where real-world data are unavailable or difficult to obtain (see Table 4-2 for the process of performing a statistical simulation). Because meta-analyses of AEs are typically based only on reported data (77), we wanted to assess how different selection criteria for reporting might impact the results of meta-analyses. We did this for one "realistic" scenario based on the small number of trials and participants typically included in Cochrane reviews (231-233) and one "ideal" scenario based on a large number of trials and participants:

1. "Realistic" scenario: meta-analyses of few (10), smaller (100 participants per arm), two-arm RCTs;
2. "Ideal" scenario: meta-analyses of many (50), large (1000 participants per arm), two-arm RCTs.

Within each of these scenarios, we:

- Varied the numerical threshold for reporting AEs while holding constant the other components of selection criteria (i.e., participant group, difference in frequency threshold, and statistical significance threshold);
- Varied the specified "true" proportion of participants expected to experience the AE across all arms; once the true proportion is specified, each simulated trial estimates the proportion of participants with an AE in a distribution centered around the true proportion. For example, if the specified true proportion is 5%,

the trials may estimate that the AE occurs in 4%, 5%, or 6% of participants in a trial because the trial is only a sample of all potential participants. As sample size increases, estimates become more precise;

- Set the odds ratio (OR) comparing two intervention groups equal to three (OR=3) for all simulations. We used an OR because meta-analyses of other types of effect estimates (e.g., relative risk, absolute risk difference) are more biased for rare events (64). We selected OR=3 because an OR=3 indicates that the AE is likely to be positively associated with an intervention (234-237);
- Assessed the average number of studies in each simulation that reported data, for each true proportion and numerical threshold for reporting;
- Plotted the average meta-analytic estimate and 95% confidence interval for (1) all studies and (2) studies that reported data about the AE using each numerical threshold for reporting, grouped by true proportion.

All parameters for our simulations are described in Table 4-3. We performed all analyses using Stata 14 (92) and R 3.3.1 (238).

Results

Search results

We identified reporting 21 gabapentin trials in 74 sources and reporting 7 quetiapine trials in 50 sources. Nearly all the sources we identified were public: 68/74 (92%) for gabapentin and 46/50 (92%) for quetiapine. One trial had no public sources (1/21 gabapentin trials).

Reporting of AE selection criteria

Selection criteria for reporting an AE varied widely across sources:

- We identified five different **numerical thresholds**: we identified four in gabapentin sources (1%, 2%, 3%, and 5%) and two in quetiapine sources (5% and 10%).
- Both gabapentin and quetiapine sources reported AEs in a variety of **participant groups**: participants in any intervention group, participants receiving gabapentin or quetiapine, and all trial participants.
- For **difference in frequency threshold**, gabapentin sources either didn't require any difference in frequency or required that AE frequency should be "higher" in the gabapentin group than the placebo group. Quetiapine sources either didn't require a difference in frequency or required that AE frequency should be "at least twice as high" in the quetiapine group as the placebo group.
- **Statistical significance** of the difference between intervention groups in the proportion of trial participants with a specific AE was not required for reporting in any source about either gabapentin or quetiapine.

These components were combined in various ways to define different selection criteria (Figure 4-1). For example, we identified a gabapentin source that reported including AEs that occurred in 1% of all participants with no additional required difference in frequency or statistical significance.

Few discrepancies in reported AEs across multiple sources about the same trial(s)

When there were multiple sources describing the same trial(s), AE reporting was consistent most, but not all, of the time (Table 4-4). We identified two discrepancies between multiple sources about the same trials. We identified one discrepancy among multiple sources about the same trial(s) that reported using the same selection criteria and one discrepancy between a CSR and public sources about the same trial.

Number of trials and sources providing AE selection criteria for reporting

Many sources (19/74 [26%] gabapentin and 18/50 [36%] quetiapine sources) did not mention specific non-systematic AEs at all (i.e., either the source did not report any information about AEs or reported only the number of participants who experienced "any AE") (Figure 4-2). Other sources (8/74 [11%] gabapentin and 10/50 [20%] quetiapine sources] mentioned specific AEs, but did not provide any numerical results (e.g., reported that common AEs included dizziness and somnolence without reporting either the number or proportion of participants who experienced these AEs). Although the majority of sources reported AEs, sources reported using selection criteria to choose particular AEs to report.

One third (7/21) of gabapentin trials and all (7/7) quetiapine trials reported selection criteria in at least one source (Table 4-5). For trials that with selection criteria reported multiple sources, 1/2 (50%) gabapentin trial and 2/4 (50%) quetiapine trials reported using the same selection criteria across sources.

The choice of AE selection criteria had a large impact on AEs that would be reported

We examined the impact of selection criteria on reporting. All components of selection criteria we identified in the sources were viewed together: (1) the five numerical thresholds (1%, 2%, 3%, 5%, and 10%); (2) the three participant groups (any intervention group, gabapentin or quetiapine participants, and all trial participants); and (3) the three differences in frequency (no difference in AE frequency between intervention groups, AE frequency higher in the active intervention group than in the placebo group, and AE frequency twice as high in the active intervention group as the placebo group); recall that no sources reported requiring statistical significance as part of the selection criteria. We combined these components we identified to form 45 different selection criteria.

By applying these 45 different selection criteria to the AE data reported in the eight CSRs we identified, we determined that the selection criteria could have a large impact on the number of different AEs that would be reported (Figure 4-3). For example, there were 91 different AEs described in CSRs for study 945-224. We found that 91/91 of these AEs met the selection criteria "occurring in ≥1% of any intervention group with no required difference in frequency." On the other hand, 0/91 AEs met the selection criteria "occurring in ≥10% of all participants with no required difference in frequency." Within the CSRs we examined, including the associated protocols, we did not identify any pre-specification of which AEs would be reported or selection criteria for reporting.

Simulations of meta-analyses indicate that certain selection criteria may lead to biased estimates of intervention effects

Figures 4-4 (“realistic” scenario) and 4-5 (“ideal” scenario) show the meta-analytic effect estimates for different proportions of participants who would have experienced the AE (“true proportions”), varying the numerical threshold for reporting, one component of selection criteria for reporting.

For each scenario (“realistic” and “ideal”), there were 5 simulations for which the specified true proportion of AEs was equal to the numerical threshold for reporting. For both scenarios, a little more than half of the studies reported AE data for each of these simulations. Interestingly, although the meta-analysis did not include AE data from all studies, the summary effect estimate and confidence interval were very similar to that when AE data all studies were included in the meta-analysis.

For each scenario (“realistic” and “ideal”), there were 10 simulations for which the specified true proportion of AEs was lower than the numerical threshold for reporting (e.g., the true proportion was 1% and the numerical threshold for reporting was 2%). In the “realistic” scenario, 8/10 simulations resulted in few trials reporting non-systematic AE data; in the remaining 2/10 simulations, no trials reported non-systematic AE data. In the “ideal” scenario, 3/10 simulations resulted in few trials reporting non-systematic AE data; in the remaining 7/10 simulations, no trials reported non-systematic AE data.

When few studies reported AE data, the resulting lack of precision sometimes led the 95% confidence interval to include an OR of 1, indicating no evidence of an effect on AEs. Thus, meta-analyses based on reported data sometimes incorrectly showed that there was no evidence of a relationship between the intervention and the AE, when there was a positive association. When no studies reported AE data, no meta-analysis could be conducted. In both scenarios, these problems happened more frequently when the specified true proportion was lower.

Discussion

Previous research has shown that non-systematic AEs are often unreported in public sources (38, 39, 46, 48, 50, 69, 88, 89, 220), but we are unaware of any research that investigates selection criteria for reporting non-systematic AEs. Although some sources did not report any selection criteria, we found a wide variety of reported selection criteria, both for each trial (across the multiple published sources available for many trials) and across trials. All of the selection criteria we identified reported using a numerical threshold (e.g., 5%) to determine which AEs to report.

We found few discrepancies between sources that reported using the same selection criteria, indicating that selection criteria were usually applied consistently. We identified a wide variety of selection criteria, however, and the choice of selection criteria can have a meaningful impact on how many non-systematic AEs would be reported. When we applied different selection criteria to the true number of non-systematic AEs that occurred in the eight trials for which we obtained CSRs, we found

that the number of different AEs that met each different selection criteria varied widely. For example, as the numerical threshold increased, fewer AEs would be reported; when the applied numerical threshold was 10%, few or no AEs would be reported. Although we had CSRs for only eight trials, the findings for each of these eight trials were consistent with each other, indicating that our results may be generalizable to other trials.

We found no evidence in the CSRs or associated protocols that the selection criteria for reporting non-systematic AEs in other sources were pre-specified. When selection criteria are not pre-specified, trialists have the opportunity to determine them *post hoc* and thus can "cherry-pick" which and how many different non-systematic AEs they report. For example, trialists could perform an analysis similar to ours in which they apply different selection criteria to their data, and then determine which selection criteria would allow them to report and not report particular AEs. The Final Rule combats this problem by requiring all trials to use the same selection criteria for reporting non-systematic AEs in ClinicalTrials.gov (5).

We found that using numerical thresholds, such as those we observed in sources about gabapentin and quetiapine, to select non-systematic AEs for reporting often leads to either inaccurate meta-analysis results (i.e., incorrectly concluding that there is no evidence of a relationship between the intervention and the AE) or an inability to perform meta-analyses because no data were reported. In our simulations, we found this to be true whether we assumed a "realistic" scenario and an "ideal" scenario; the problems we observed (i.e., few or no trials reporting AE data) were not alleviated by

having large, high-quality primary studies. Because of the consistency of our findings, we believe that using numerical thresholds to select non-systematic AEs for reporting is problematic, regardless of the intervention, condition, or trial characteristics. Our findings were also consistent with the existing evidence about the effect of outcome reporting bias on effectiveness outcomes; selectively reporting effectiveness outcomes based on their quantitative results can lead to biased meta-analysis results (65-68).

In our simulations, we found that meta-analyses of rarer AEs (e.g., occurring in about 1% of participants) were more likely to be inaccurate because of numerical thresholds for reporting; this is because rarer AEs were more likely to be excluded from reporting based on numerical thresholds. Because trials are typically not powered to detect differences between intervention groups in the how often AEs occur (72), meta-analyses of AE data from multiple trials provide an opportunity to detect true differences in the frequency of AEs, which are often rare (64). Thus, rare AEs, which are most likely to benefit from meta-analyses, are also most likely to be unreported when trials report AEs based on a numerical threshold.

Although most reporting of non-systematic AEs appears to be based on a numerical threshold for reporting, patients are not necessarily most interested in the AEs that occur the most frequently(239). Most patients report that they would like to know information about *all* AEs when selecting a health intervention (239, 240), while others indicate that they wanted information about serious AEs that will have an impact on quality of life (241). The importance of serious AEs to patients appears to be recognized by the Final Rule, which requires the reporting of serious AEs in addition to

frequent AEs (i.e., occurring in ≥5% of any treatment group). Other rare non-systematic AEs are still excluded from their reporting guidelines, however. Healthcare has been evolving to emphasize the preferences of patients (2, 242), and patient preferences should be incorporated into the collection and reporting of AEs.

Based on our research, we have several recommendations about non-systematic AEs. First, data about all AEs should be made available to the public, including patients, systematic reviewers, and other healthcare stakeholders. Moving forward, trialists should report data about all AEs. For example, journals could require trialists to submit an online supplement that contains data about all AEs to accompany the journal article reporting trial results. It may not be feasible to report all AEs in some sources, such as conference abstracts that have space limitations. In those cases, reported AEs should be selected based on their importance to patients and other healthcare stakeholders, rather than their results. The source should also (1) state that only a subset of AEs are reported and (2) direct readers where to find data about additional AEs. For older trials that have already been incompletely published, making data about all AEs public may involve sharing sources that are typically unavailable to the public, such as CSRs. Although there are currently data-sharing efforts underway, many of these initiatives apply only to trials completed after a particular date (78-80). If trialists choose to select AEs for reporting based on their quantitative results, all four components of the selection criterion should be pre-specified to minimize opportunities for cherry-picking. Regardless of how AEs are selected for reporting, selection criteria should be reported alongside the AEs to promote transparency.

Systematic reviewers should be aware of the potential problems of using AEs reported based on their quantitative results. When systematic reviewers encounter sources that report selecting AEs based on their quantitative results, they should request additional data from trial authors. If data are not made available, systematic reviewers should interpret any AE meta-analysis results with extreme caution and discuss the limitations of using only publicly available data.

According to the National Academy of Medicine, clinical practice guidelines should be based on high-quality systematic reviews of the evidence (243). Systematic reviews and meta-analyses are typically based on publicly reported data (77). This means that, based on our findings, guideline developers, as well as other healthcare stakeholders, may be basing their recommendations on either no information or inaccurate information. Reporting a subset of AEs that occur during a trial, particularly if they are chosen for reporting based on a numerical threshold rather than their importance to patients and other healthcare stakeholders, is problematic for guideline developers, clinicians, and patients. Having the best possible evidence about a health intervention is important to those making healthcare decisions. For some conditions, such as depression, there may be many interventions available (244). Without accurate evidence about the potential benefits and AEs of each intervention, patients may have to try several different interventions to find one that is beneficial and does not cause any AEs, putting them at risk from both the multiple interventions and their underlying condition. Improved transparency of the potential AEs of interventions through data-

sharing and open science would subsequently enable healthcare stakeholders to make decisions based on all available evidence, rather than on selectively reported data.

Table 4-1. Glossary of Terms

Term	Definition
Adverse events	
Adverse event	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (19).
Non-systematic adverse events (Final Rule)[1]	Adverse events that are collected using open-ended questions or are spontaneously reported by participants (i.e., non-systematically collected). For example, adverse events obtained by asking participants questions like "Have you noticed any symptoms since your last examination?" (5).
Systematic adverse events (Final Rule)[1]	Adverse events that are collected in the same manner for each participant using methods related to specific adverse events (i.e., systematically collected). For example, adverse events collected using validated questionnaires, checklists, laboratory measurements, or vital signs (5).
Selection criteria	Methods described in a data source as used to choose which AEs are reported in that source.
Sources	
Public sources[1]	In this study, public sources include journal articles, conference abstracts, commentaries, posters, trial registrations and associated results, and medical and statistical reviews created by the Food and Drug Administration.
Non-public sources[1]	In this study, non-public sources include clinical study reports and clinical study report-Synopses.
Clinical study report (CSR)[1]	A comprehensive document created by a pharmaceutical company detailing the design, methods, analyses, and results of a single study for submission to regulatory agencies. CSRs are often thousands of pages in length. Appendices contain tables of individual participant data, also called "patient data listings."
Clinical study report Synopsis (CSR-Synopsis)[1]	An internal company document that summarizes the information contained in CSRs. CSR-Synopses are much shorter than CSRs; our two CSR-Synopses were each 13 pages in length.

[1] Item adapted from our previous research on AE reporting (220, 230).

Table 4-2. Process of statistical simulations

Table 4-2 Legend: A *simulation* uses computer-generated data to model events to approximate real-world outcomes in cases where real-world data is unavailable or difficult to obtain. We have used simulations to model the effect of using different selection criteria on meta-analyses of randomized controlled trials (RCTs). We have adapted the steps for completing a simulation from previous research (245).

Steps of performing a statistical simulation	**Our simulations as an example**
Clearly state the problem.	How is a meta-analysis of a specific adverse event likely to be affected if it is based on data that have been selected for reporting, rather than all data that have been collected?
Define the components which form the basis of the simulation.	We are simulating meta-analyses, which are made up of multiple components in this simulation: Occurrence of the adverse event within the included trials, defined by the proportion of all participants who experienced the AE and the relative association of the two intervention arms (i.e., odds ratio [OR]). Numerical threshold for reporting, which we specified in our simulations based on numerical thresholds for reporting we identified in the literature. Number of included trials and participants in each meta-analysis.
State the underlying assumptions and select a model.	We assumed that the adverse event occurred in each trial following a binomial distribution with a specified probability. Our meta-analytic estimates of effect used the OR as a measure of association estimated using the Mantel-Haenszel method (246).
Simulate a single iteration and record the outcomes of interest.	For each iteration, we recorded the meta-analytic estimate and 95% confidence interval.
Repeat step four.	We performed step four 1000 times.
Summarize the information and draw conclusions.	We averaged the results of our 1000 simulated observations to get an overall meta-analytic estimate of the OR and 95% confidence interval.

Table 4-3. Fixed and varied parameters in simulations of meta-analyses of RCTs

Description of parameter	Value(s)	Rationale for parameter selection
Parameters fixed in each scenario		
Number of participants per arm in each RCT	100, 1000	A typical RCT included in a Cochrane systematic review has about 100 participants (231); we selected 1000 as a large sample size for comparison.
Number of RCTs in each meta-analysis	10, 50	A typical Cochrane systematic review includes 10 or fewer studies (231-233); we selected 50 as a large number of included trials for comparison.
Parameters fixed across scenarios		
Specified odds ratio of experiencing the adverse event in RCT	3	We selected a positive association between the adverse event and the intervention (234-237).
Number of simulated meta-analyses	1000	Standard number of iterations for a simulation.
Number of arms in each RCT	2	Standard number of arms in an RCT.
Parameters varied in each scenario		
"True" proportion of all participants in RCT with AE	1%, 2%, 3%, 5%, 10%	We observed these numerical thresholds for reporting in the eligible trials of this study.
Selection criterion/numerical threshold for proportion of all participants with AE required for reporting	1%, 2%, 3%, 5%, 10%	We observed these numerical thresholds for reporting in the eligible trials of this study.

Table 4-4. Comparison of adverse events reported in sources about the same trial

Table 4-4 Legend: This table shows two types of comparisons we made. We first compared multiple sources about the same trial(s) that reported using the same selection criteria. We then compared data in the clinical study reports (CSRs), which reported all adverse events (AEs), with sources that reported selection criteria. A trial may appear in both sections if we identified both (1) multiple sources that reported using the same selection criterion and (2) a CSR for that trial. For example, we identified two sources that reported selection criteria as well as a CSR for Rice 2001, so Rice 2001 appears in both sections of the table.

[1] Note that this section of the table does not include CSRs. CSRs are required to report summary data for all AEs, so they do not utilize selection criteria.

Trial	Reported selection criteria	Were sources consistent with each other?
Sources about the same trial reporting the same adverse event (AE) selection criteria, when there were multiple sources[1]		
Rice 2001	≥5% patients (129, 132)	Yes
Sang 2013 and Wallace 2010	≥3% gabapentin patients (152); ≥3% patients in any trial arm (150, 151)	No: one source (152) reported one additional AE (150, 151)
Calabrese 2004	≥10% of quetiapine patients and twice as frequent in quetiapine patients, compared with placebo patients (184-186, 195)	Yes
McElroy 2010	≥5% patients in any trial arm (202, 204)	Yes
Young 2008	≥5% patients in any trial arm (216, 218)	Yes
Source(s) about the same trial reporting any AE selection criteria compared with CSR about the same trial		
Rice 2001	>5% patients (130) (129, 132)	No: two sources (129, 132) reported data for two additional AEs; based on information in the CSR (130), we believe the sources reported AEs occurring in 5% of gabapentin-treated patients
Serpell 2002	≥5% gabapentin patients (158, 160)	Yes
Calabrese 2004	≥10% of quetiapine patients and twice as frequent in quetiapine patients, compared with placebo patients(184-186, 195); ≥10% patients in any trial arm (182, 194)	Yes
Thase 2006	≥10% patients in any trial arm (210, 212)	Yes

Table 4-5. Number of different adverse event selection criteria across sources about the same trial

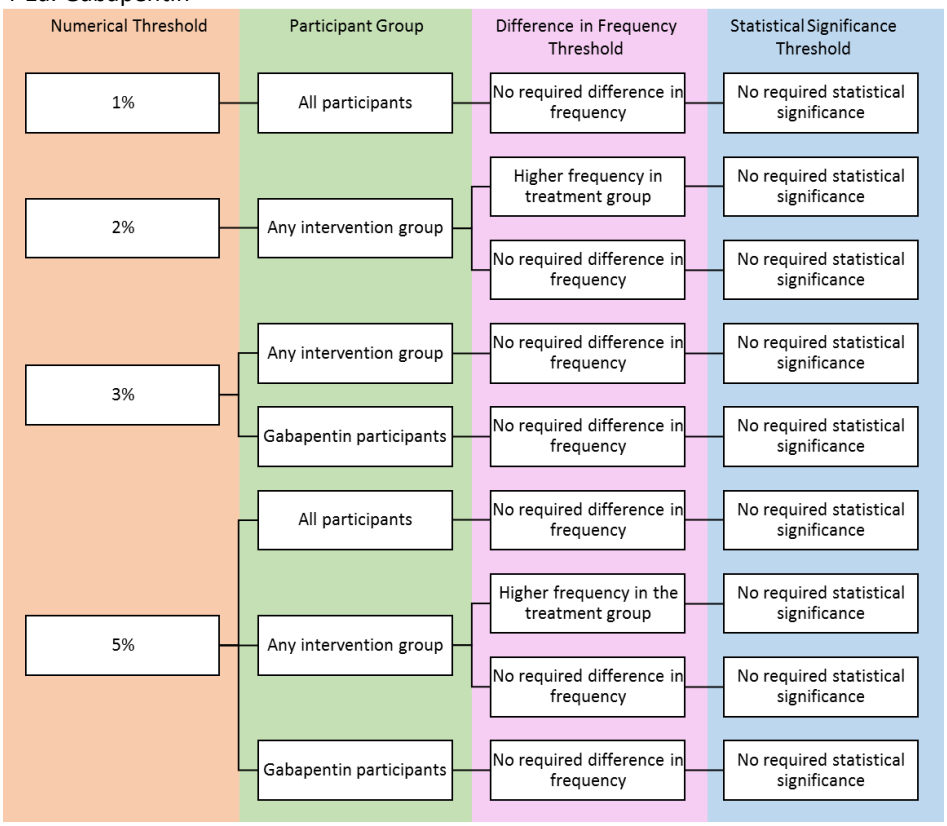
Table 4-5 Legend: This table only includes sources about a single trial.

	Gabapentin (21 trials)	Quetiapine (7 trials)
Trials with no reported selection criteria in sources about a single trial	14	0
Trials with selection criteria reported in ≥1 source about a single trial	7	7
Trials with selection criteria reported in 1 source	5	3
Trials with selection criteria reported in >1 source	2	4
Trials with same selection criteria reported across all sources	1	2
Trials with ≥2 different selection criteria reported across sources	1	2

Figure 4-1. Observed components of reported adverse event selection criteria

Figure 4-1 Legend: This figure shows the selection criteria we observed in sources about gabapentin (4-2a) and quetiapine (4-2b). The four components of selection criteria are shown in separate columns. For example, the first row of boxes shows the selection criteria, "occurring in ≥1% of all participants with no requirements for difference in frequency or statistical significance."

4-1a. Gabapentin



4-1b. Quetiapine

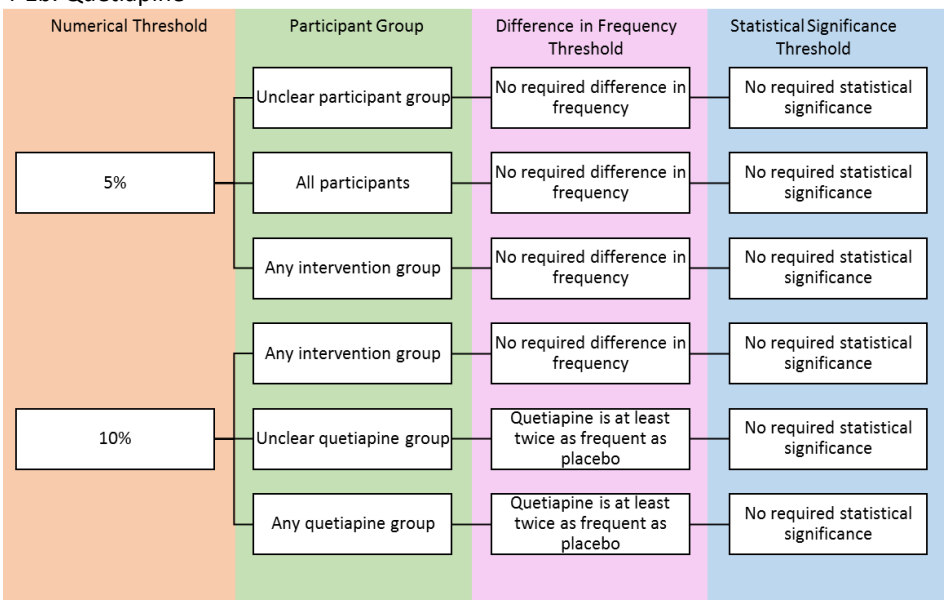


Figure 4-2. Reported adverse events and adverse event selection criteria

Figure 4-2 Legend. "Results" refer to any reported adverse event (AE) data (e.g., number or proportion of participants who experience an AE). "Selection criteria" refers to the reported methods for choosing which AEs to report.

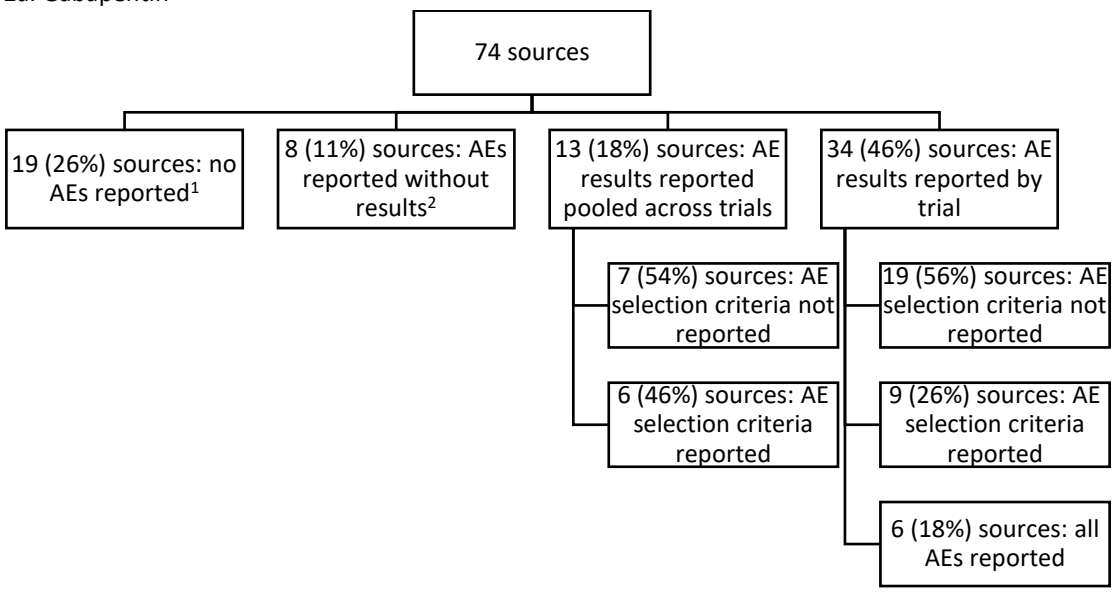
[1] 12 gabapentin sources with no AEs were about a single trial; 7 gabapentin sources with no AEs were about multiple trials.

[2] 7 gabapentin sources with no AE results were about a single trial; 1 gabapentin source with no AE results was about multiple trials.

[3] 13 quetiapine sources with no AEs were about a single trial; 5 quetiapine sources with no AEs were about multiple trials.

[4] 8 quetiapine sources with no AE results were about a single trial; 2 quetiapine sources with no AE results were about a multiple trials.

4-2a. Gabapentin



4-2b. Quetiapine

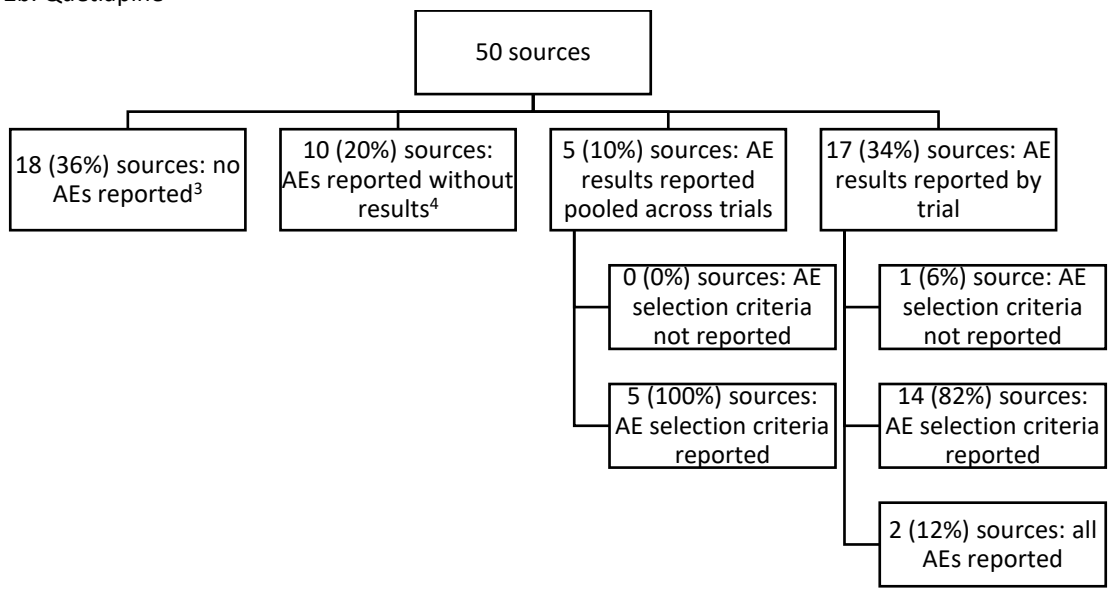


Figure 4-3. Number of different adverse events that would be reported using different selection criteria

Figure 4-3 Legend: We applied 45 different selection criteria to the data in each of the eight trials for which we identified clinical study reports (CSRs) and calculated the number of different adverse events (AEs) that met each of the selection criteria. For example, in study 945-224, 78 different AEs would be reported if the applied selection criterion is "≥1% of patients receiving gabapentin, with no additional different in magnitude." Note that the "active" intervention group refers to either gabapentin or quetiapine, rather than placebo.

To illustrate the potential variation in reported non-systematic AEs for each trial, we used a heat map to depict the number of different AEs that would be reported assuming less and more inclusive selection criteria. Numbers in the green squares depict the non-systematic AEs that would be reported assuming the most inclusive selection criteria, numbers in the yellow squares depict the non-systematic AEs that would be reported assuming moderately inclusive selection criteria and the numbers in red squares depict the non-systematic AEs that would be reported assuming the least inclusive selection criteria), for each trial. Squares outlined in **black** represent the selection criteria used in at least one source about that trial (e.g., a source describing Serpell 2002 reported nine different non-systematic AEs that occurred in ≥5% of gabapentin participants with no additional criteria related to difference in frequency between groups). Some trials did not have any sources that described the selection criteria (e.g., 945-224).

A No difference in frequency of AEs observed in the gabapentin/quetiapine and placebo groups; **B** Higher frequency in gabapentin/quetiapine than in placebo; **C**= Frequency in gabapentin/quetiapine at least twice as high as placebo; [1]Gabapentin trial; [2]Quetiapine trial

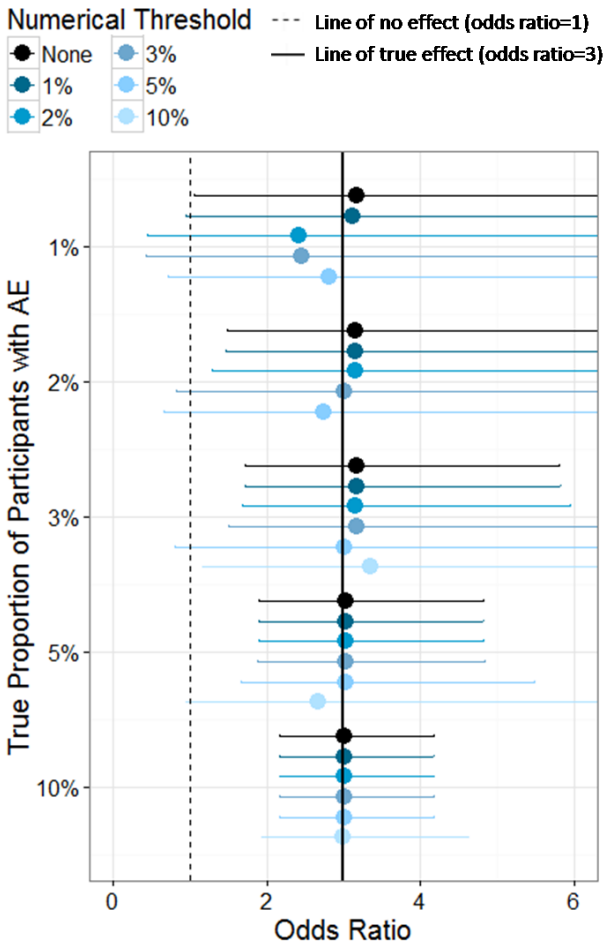
Number of different non-systematic adverse events reported using each combination of selection criteria												
	Difference in frequency threshold for reporting AEs											
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Numerical threshold and participant group	Trial identifier											
	945-224[1]			A945-1008[1]			Backonja 1998[1]			Rice 2001[1]		
No selection criteria (CSR)	91			198			96			108		
1% any intervention group	91	59	52	76	38	26	95	57	53	43	32	26
1% active intervention group	78	59	52	50	38	26	75	57	53	34	32	26
1% all participants	21	17	10	60	36	24	45	22	18	29	23	17
2% any intervention group	26	20	13	34	23	16	37	22	18	28	22	17
2% active intervention group	23	20	13	28	23	16	28	22	18	24	22	17
2% all participants	12	9	4	29	20	13	20	13	9	14	12	9
3% any intervention group	15	12	6	24	17	14	22	14	10	17	13	10
3% active intervention group	13	12	6	19	17	14	18	14	10	15	13	10
3% all participants	7	6	4	16	11	8	18	11	7	10	8	7
5% any intervention group	8	6	4	8	7	6	12	9	7	10	8	7
5% active intervention group	6	6	4	7	7	6	9	9	7	8	8	7
5% all participants	2	2	2	8	7	6	7	5	3	**4**	4	3
10% any intervention group	1	1	1	4	4	4	5	4	3	3	3	3
10% active intervention group	1	1	1	4	4	4	4	4	3	3	3	3
10% all participants	0	0	0	3	3	3	2	2	2	2	2	2

	Rowbotham 1998[1]			Serpell 2002[1]			Calabrese 2004[2]			Thase 2006[2]		
No selection criteria (CSR)	122			111			316			273		
1% any intervention group	47	28	24	56	35	24	126	86	67	123	74	57
1% active intervention group	38	28	24	47	35	24	117	86	67	100	74	57
1% all participants	36	22	18	32	19	11	77	54	43	65	41	24
2% any intervention group	28	19	15	26	16	11	67	50	42	58	39	22
2% active intervention group	25	19	15	24	16	11	59	50	42	49	39	22
2% all participants	19	12	8	20	11	6	37	27	21	34	26	15
3% any intervention group	16	12	8	21	13	9	33	26	20	30	22	14
3% active intervention group	15	12	8	18	13	9	31	26	20	28	22	14
3% all participants	15	9	5	12	6	2	21	16	11	23	15	9
5% any intervention group	7	5	5	11	6	2	17	13	11	21	14	9
5% active intervention group	5	5	5	**9**	6	2	17	13	11	18	14	9
5% all participants	7	4	4	9	5	2	12	8	6	13	9	5
10% any intervention group	2	2	2	4	2	2	**9**	6	5	**8**	6	5
10% active intervention group	2	2	2	2	2	2	7	6	**5**	7	6	5
10% all participants	2	2	2	3	1	1	5	4	4	6	4	4

Figure 4-4. Simulations of meta-analyses of 10 trials with 100 participants in each arm

Figure 4-4 Legend: For each simulation, we ran 1000 iterations of meta-analyses of 10 trials with 100 participants in each arm. We plotted the mean of these 1000 meta-analytic estimates with 95% confidence intervals for all studies (i.e., no numerical threshold for reporting) and studies that would be reported using each of five numerical thresholds for reporting. When the numerical threshold for reporting was higher than the true proportion, few studies reported AE data. Fewer studies led to a wider confidence interval, sometimes causing it to cross the null. Note that estimates are more precise for more common events, so the width of the confidence intervals decreased as the true proportion increased; this is a function of meta-analytic estimates (247).

AE=Adverse event; *When the mean number of included studies is <1, some meta-analyses in that simulation would not include any data from any studies, while other meta-analyses would include data from 1-2 studies.

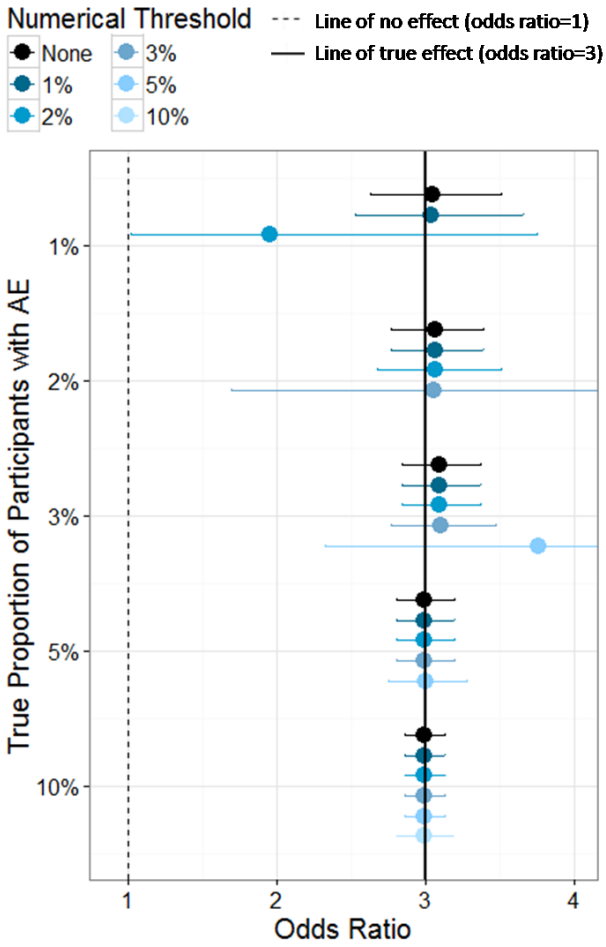


Mean Number of Studies Included in Meta-Analysis (maximum of 10)					
No Numerical Threshold (All Studies)	**1%**	**2%**	**3%**	**5%**	**10%**
10	6	1	< 1*	< 1*	0
10	9	6	2	< 1*	0
10	10	9	6	< 1*	< 1*
10	10	10	9	6	< 1*
10	10	10	10	10	5

Figure 4-5: Simulations of meta-analyses of 50 trials with 1000 participants in each arm

Figure 4-5 Legend: For each simulation, we ran 1000 iterations of meta-analyses of 50 trials with 1000 participants in each arm. We plotted the mean of these 1000 meta-analytic estimates with 95% confidence intervals for all studies (i.e., no numerical threshold for reporting) and studies that would be reported using each of five numerical thresholds for reporting. In most cases where the numerical threshold for reporting was higher than the true proportion, no studies reported AE data, so no meta-analytic estimate could be calculated. Note that estimates are more precise for more common events, so the width of the confidence intervals decreased as the true proportion increased; this is a function of meta-analytic estimates (247).

AE=Adverse event; *When the mean number of included studies is <1, some meta-analyses in that simulation would not include any data from any studies, while other meta-analyses would include data from 1-2 studies.



Mean Number of Studies Included in Meta-Analysis (maximum of 50)

No Numerical Threshold (All Studies)	1%	2%	3%	5%	10%
50	27	< 1*	0	0	0
50	50	26	< 1*	0	0
50	50	50	26	< 1*	0
50	50	50	50	26	0
50	50	50	50	50	26

Appendix 4-1. Detailed methods

Identifying sources about eligible trials

We searched both the International Clinical Trials Registry Platform Search Portal (ICTRP) and ClinicalTrials.gov for trial registrations and associated results related to gabapentin or quetiapine on October 10, 2014. We searched PubMed, Embase, Lilacs, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) for gabapentin and quetiapine sources, as well as PsycInfo for quetiapine; we completed our searches March 2, 2015 (gabapentin) and January 26, 2015 (quetiapine), without any language restrictions. We identified medical and statistical reviews of gabapentin as well as quetiapine available on the FDA website (26). We also searched certain conference proceedings and years for gabapentin trials (see protocol (81)). We searched online (http://psychrights.org/) for typically non-public sources about quetiapine for bipolar depression. We requested non-public sources in the form of internal company documents from the manufacturers of gabapentin and quetiapine (Pfizer and AstraZeneca, respectively). We identified the trial(s) reported in each source and grouped sources by the trial(s) described.

Appendix Table 4-1. Sources about eligible trials

Gabapentin Trials
945-224 (96-101)
A945-1008 (102)
Arai 2010 (103, 104)
Bakonja 1998 (96-100, 105-113)
Caraceni 2004 (114-116)
Hahn 2004 (117)
Hui 2010 (118, 119)
Irving 2009 (120, 121)
Milenkovic 2009 (122)
Mishra 2012 (123)
NCT00475904 (124)
Rice 2001 (96-100, 125-132)
Rowbotham 1998 (96-100, 125-128, 133-136)
Sandercock 2012 (137-139)
Sang 2013 (140-156)
Serpell 2002 (96-100, 128, 157-160)
Simpson 2001 (161, 162)
Tamez Pérez 2000 (163, 164)
Wallace 2010 (140-152, 165-167)
Yildirim 2003 (168)
Zepeda Vazquez 2001 (169)
Quetiapine Trials
Calabrese 2004 (170-195)
Gao 2014 (196, 197)
Li 2014 (198, 199)
McElroy 2010 (170-176, 200-204)
Suppes 2010 (205-207)
Thase 2006 (170-180, 208-213)
Young 2008 (170-176, 200, 214-219)

Chapter 5. Conclusions

Summary

Adverse events (AEs) are an important consideration when selecting a health intervention. Some AEs (e.g., serious AEs, "death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (19, 20)) can have severe medical consequences, and even seemingly minor AEs can result in patients discontinuing the intervention. It is therefore vital for healthcare stakeholders to be aware of the potential AEs associated with an intervention and to be able to compare the risk of AEs across different health interventions.

Although regulatory agencies such as the Food and Drug Administration (FDA) typically have access to clinical study reports (CSRs) and individual patient data (IPD) for randomized controlled trials (RCTs) , not all RCTs are submitted to regulatory agencies, and other healthcare stakeholders often do not have access to these types of sources.

The objective this dissertation was, to describe, in three specific aims the extent to which data about AEs are unavailable to healthcare stakeholders, typically with access to only public sources, and to assess how unreported data might impact systematic reviews and meta-analyses based on public sources. Here, we summarize our findings and describe the implications of each of the three aims, as well as draw overall conclusions, make recommendations, and propose possible future directions for research.

Aim 1

Using RCTs examining gabapentin for neuropathic pain or quetiapine for bipolar depression, (a) compare the reporting of non-systematic AEs across all available sources (i.e., abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD) about RCTs and (b) assess how reporting patterns affect which evidence meta-analyses would be based on.

In Aim 1, we described the reporting of non-systematic AEs in 80 sources about 21 gabapentin trials and 52 sources about 7 quetiapine trials. We identified non-public sources for only 6/21 gabapentin trials and 4/7 quetiapine trials. We found that nearly all AEs were collected using non-systematic methods. In addition, data about the majority of non-systematic AEs were available only in non-public sources. For example, 341/419 (81%) and 436/471 (93%) different AEs were available only in non-public sources, for gabapentin and quetiapine, respectively. Thus, in most cases, healthcare stakeholders interested in information about non-systematic AEs would not expect to be able to find it in public sources, and would have to base healthcare decisions on little or no evidence. This is particularly problematic for serious AEs, which represent important risks for patients. We found that the majority of serious AEs were reported only in non-public sources: 56/72 (78%) in gabapentin trials and 39/46 (85%) in quetiapine trials. Our findings were consistent in both of our case examples.

Systematic reviews and meta-analyses present the opportunity to combine information about rare events, because outcomes are synthesized from all relevant trials. Such synthesis is crucial for non-systematic AEs specifically, because RCTs are not usually powered to detect differences in the frequency of non-systematic AEs between intervention groups (72). Yet, we found that, even when non-systematic AEs were reported, they were not always reported completely (e.g., either the number of people who experienced the AE or the number of people in the analysis was not reported). This means that (1) patients and clinicians cannot determine the likelihood that someone will experience an AE on a particular intervention and (2) the data from these RCTs cannot be synthesized in a meta-analysis or effectively compared with RCTs on other interventions. Without this information, policy-makers cannot develop evidence-based clinical practice guidelines and patients and clinicians must make healthcare decisions without knowing crucial information about the relative safety of their intervention options.

Aim 2

Using RCTs examining quetiapine for bipolar depression, (a) compare the reporting of systematic AEs across all available sources (i.e., abstracts, journal articles, clinical trial registries, FDA reviews, CSRs, CSR-Synopses, and IPD) about RCTs, (b) describe the completeness of reporting for systematic AEs in each data sources, and (c) assess how reporting patterns affect which evidence meta-analyses would be based on.

When AEs are suspected of being related to an intervention, RCT investigators may elect to collect data about these AEs systematically. In our research, nearly all of the AE data we identified were collected non-systematically, rather than systematically. Although we planned to examine systematic AEs in both case examples (gabapentin and quetiapine), we did not identify any systematically collected AEs in the gabapentin for neuropathic pain RCTs. Therefore, the results of our second aim were based solely on the data from the quetiapine for bipolar depression RCTs. We identified non-public sources for only 4/7 quetiapine trials.

Only one of our six pre-specified systematic AE outcome domains (mania) was reported in any source for all seven eligible RCTs; the remaining outcome domains were reported in only a subset of eligible RCTs. Failure to report systematic AEs publicly and completely means that healthcare decisions are based on selected subset of all information. Because systematic AEs are selected for collection based on their suspected association with the intervention, their collection and reporting is particularly important.

We found that many systematic AEs reported in public sources were not fully-defined (i.e., one or more of the elements of an outcome were not described). In addition, many results found in public sources were not “meta-analyzable” (i.e., reported in enough detail to be included in a meta-analysis). In contrast, nearly all of the outcomes found in non-public sources were fully-defined and their results were meta-analyzable. For example, more than half (90/159; 57%) of results reported in public sources were both meta-analyzable and associated with defined outcomes, compared

with nearly all (310/636; 96%) results reported in non-public sources. When data are incompletely reported, healthcare stakeholders are unable to synthesize data from multiple trials or compare the relative effect of different health interventions on systematic AEs.

Although the FDA suggests that "[p]otential problems that may be suspected because of preclinical data or because of effects of related drugs should be targeted for evaluation" (13), we have been unable to identify guidance about which AEs should be collected systematically or what measurement tools should be used to collect these systematic AEs. This may lead to inconsistency in the AE outcomes collected across trials, which, in turn, complicates synthesizing RCTs or comparing results from RCTs of different interventions. To improve consistency across RCTs, we propose the development of core outcome sets (23, 24) specifically related to AEs.

We propose that more AEs should be collected using systematic methods. Systematic methods utilize instruments, such as questionnaires or measurement tools (e.g., scales to measure weight), to assess information about AEs. The validity and reliability of these instruments can be assessed using well-established methods (222-224). In contrast, non-systematic methods do not utilize instruments, and we are unaware of any methods for assessing the validity or reliability of non-systematic methods. Because validity and reliability are important indicators of the quality of research (222), using valid and reliable methods to systematically collect AEs will improve the overall quality of healthcare research.

Aim 3

Using RCTs examining gabapentin for neuropathic pain or quetiapine for bipolar depression, (a) compare reported methods for selecting which non-systematic AEs to report both across multiple trials and across multiple sources for the same trial, (b) compare the non-systematic AEs reported in different sources that report using the same methods for selecting AEs for reporting, and (c) use simulated data to assess how using different "selection criteria" impacts the results of meta-analyses.

In Aim 3, we compared the reported methods for selecting non-systematic AEs for inclusion in sources ("selection criteria") about gabapentin for neuropathic pain and quetiapine for bipolar depression. As we found in Aim 1, non-systematic AEs were frequently unreported in the sources we identified. The new information related to this aim is that failure to report non-systematic AEs may be related to the selection criteria for reporting. Often, sources that reported non-systematic AEs did not report how trial investigators determined which non-systematic AEs to report. When sources did describe how non-systematic AEs were selected for reporting, we identified a wide variety of reported selection criteria, both across trials and across different sources about the same trial(s). All of the selection criteria we identified reported selecting non-systematic AEs based on a numerical threshold for reporting, rather than their importance to patients or other healthcare stakeholders.

When multiple sources about the same trial(s) reported using the same selection criteria, we compared which AEs were reported in each source. We found rare

discrepancies; different sources, including CSRs, about the same trial(s) were generally consistent with each other. For example, if multiple sources about the same trial(s) reported that they included all non-systematic AEs occurring in ≥5% of all participants, the sources typically reported the same AEs.

We found no evidence that the selection criteria used in the identified trials were pre-specified. Using different selection criteria had a large impact on the number of different non-systematic AEs that would be reported. For example, there were 91 different AEs described in CSRs for study 945-224. We found that 91/91 of these AEs met the selection criteria "occurring in ≥1% of any intervention group with no required difference in frequency." On the other hand, 0/91 AEs met the selection criteria "occurring in ≥10% of all participants with no required difference in frequency." If selection criteria are not pre-specified, trialists could "cherry-pick" which and how many non-systematic AEs to report and then identify the selection criteria that would allow them to report those AEs.

Even if trialists do pre-specify selection criteria, we found using selection criteria based on a numerical threshold for reporting can lead to significant problems. Selecting AEs for reporting based on a numerical threshold for reporting can lead to meta-analyses of publicly reported AE data incorrectly showing no evidence of effect. Sometimes, meta-analyses cannot be performed at all. This is particularly problematic because most meta-analyses of AEs are based on publicly reported data (77). Our findings are consistent with evidence that suggests outcome reporting bias (58-63)

Overall conclusions and future directions

Based on the results of this dissertation, we believe there is cause for concern about the collection and reporting of AEs. Our evidence suggests that most AEs are collected non-systematically, and both non-systematic and systematic AEs, including serious AEs, were frequently unreported in public sources. In addition, we have shown that the non-systematic AEs were typically selected for publication based on the direction and nature of their quantitative results, which can impact the results of meta-analyses based on these reported results. We have recommendations for trialists and systematic reviewers (Box 5-1), as well as recommendations for future AE research. Our recommendations for future research are:

More research can be done examining design, operations and reporting for other interventions and indications to understand the general applicability of our findings to other research questions. While much of our evidence is based on two case studies what we have found is generally consistent with previous research (45-50, 69).

Further research is needed about the reporting of systematic AEs, including the consistency of data collection of systematic AEs across trials. It is important to understand which AEs are collected systematically in trials and to assess how AE collection evolves over time as more becomes known about the potential harms of an intervention; improved access to typically non-public sources will allow researchers to assess the consistency of AE collection across trials.

More research is needed to develop core outcome sets specifically devoted to AEs. One of the main goals of core outcome sets is to improve consistency across trials to promote synthesis of trials about the same intervention and to facilitate comparison across different interventions. However, current core outcome sets have been developed with a focus on effectiveness outcomes for particular conditions (23, 24). In addition, the same intervention may have similar or different AEs when it is taken for different indications and in combination with other interventions, and this will complicate the development of core outcome sets.

We believe that the research performed as part of this dissertation highlights both problems with existing AE research and current evidence gaps. Currently, most AEs are collected non-systematically, even though systematic methods can be assessed as valid and reliable, improving the overall quality of the research. The majority of AEs, both systematic and non-systematic, are unreported in public sources. This means that patients and other healthcare stakeholders are typically unable to access the information required to make evidence-based healthcare decisions. In addition, systematic reviews and meta-analyses, which should form the basis for clinical practice guidelines (243), are likely to be inaccurate or unavailable when based on only publicly reported data about AEs. Given the results of this dissertation and previous evidence, patients, clinicians, and other healthcare stakeholders are currently lacking critical information about the safety of health interventions.

Open access to typically non-public sources will not solve all of the problems we identified. Although open access to non-public sources may facilitate meta-analyses of

currently unavailable data, there are also problems with the collection and analysis of AEs. For example, most AEs are collected non-systematically; while it is impossible to foresee all possible AEs, and therefore some non-systematic collection is necessary, known or suspected AEs should be collected systematically. In addition, there are hundreds of different non-systematic AEs. Grouping related non-systematic AEs for analysis may facilitate understanding of the likely AEs for a health intervention.

Box 5-1. Recommendations for trialists and systematic reviewers

1. Incorporate both potential AEs and potential benefits into the design (as reflected in the protocol) and reporting of an RCT.
2. Develop, regularly update, and use core outcome sets for AEs for interventions or groups of interventions (e.g., drug class).
3. Collect data on known AEs systematically, and as evidence about AEs accumulates, update which AEs are collected systematically.
4. As recommended by the FDA (13), preclinical studies, as well as trials of other drugs in the same class or other indications for the same drug should inform systematic AE collection.
5. Pre-specify and describe collection methods for all AEs in the trial protocol and provide case report forms.
6. Report collection methods for all AEs in all public sources about RCTs.
7. Report fully-defined outcomes and complete (i.e., meta-analyzable) quantitative results for AEs.
8. Make all AE data, as well as collection and analysis methods, available to the public; one potential mechanism for some RCTs is for the FDA to release the information that is submitted to them.
9. If a particular source of information about an RCT will include data about only a subset of AEs, (a) do not use selection criteria based on the numerical thresholds for reporting, (b) describe how AEs were selected for inclusion in the source, and (c) direct readers to where they can find information about the unreported AEs.
10. If, as a systematic reviewer, you encounter sources that report using quantitative results to select AEs for reporting, request data about all unreported AEs from the RCT investigator; if data is not made available, interpret your systematic review results with extreme caution.

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Curriculum Vitae

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Curriculum Vitae, September 8, 2017

Part I

Contact Information

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Education and Training

Degrees

Year	Degree	Institution	Field
2017	Doctor of Science (ScD)	Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland	Epidemiology (Clinical Trials and Evidence Synthesis)
2012	Master of Arts	Brown University, Providence, Rhode Island	Biostatistics
2009	Bachelor of Science	University of Massachusetts, Amherst, Massachusetts	Biochemistry

ScD Dissertation

Title: The Collection and Reporting of Adverse Events in Randomized Controlled Trials: Gabapentin for Neuropathic Pain and Quetiapine for Bipolar Depression as Case Examples

Advisor: Dr. Kay Dickersin

Professional Experience

Research Associate, Multiple Data Sources Project: September 2014 – Present

- Prepared manuscripts for publication.
- Analyzed efficacy and safety data.
- Created and executed data management plan for individual patient data.
- Abstracted data from journal articles, clinical study reports, and abstracts.
- Assisted with form development and analysis plans.

Pharmacovigilance and Risk Management Intern, Takeda Pharmaceuticals: June 2014 – August 2014

- Analyzed large insurance datasets.
- Prepared reports for pharmacovigilance team in the oncology division.
- Assisted in preparation of Risk Management Plans.

Research Assistant, Cochrane Eyes and Vision: September 2012 – June 2014

- Created a centralized database for articles on reporting biases.
- Performed analyses on PCORI data.
- Collected and managed data for network meta-analysis.

Analyst, Datacorp: September 2010 – August 2012

- Cleaned, managed, and analyzed data using SAS and SPSS.
- Performed literature reviews and wrote reports.
- Evaluated and reported on community intervention program performance.
- Worked on grant applications.

Direct Care Staff, Behavioral Health Network: September 2009 – August 2010

- Provided daily support for developmentally disabled and mentally ill adults.
- Passed medication, performed daily hygiene practices, and supervised health care for disabled individuals.

Direct Care Staff, Haven House: December 2007 – August 2009

- Provided personal care of developmentally disabled and mentally ill adults.
- Performed insulin injections, passed medication, and oversaw health care for disabled individuals.

Peer Review Experience

1. PLOS One
2. BMJ
3. Trials
4. Systematic Reviews
5. Ophthalmology

Peer-Reviewed Publications

1. Mayo-Wilson E, Hutfless S, Li T, Gresham G, **Fusco N**, Ehmsen J, Heyward J, Vedula S, Lock D, Haythornthwaite J, Payne JL. *Integrating multiple data sources*

(MUDS) for meta-analysis to improve patient-centered outcomes research: a protocol for a systematic review. Systematic Reviews. 2015 Nov 2; 4(1):143.

2. Mayo-Wilson E, **Fusco N**, Li T, Hong H, Canner J, Dickersin K. *Multiple outcomes and analyses in clinical trials create challenges for interpretation and research synthesis*. Journal of Clinical Epidemiology. 2017 May 18.
3. Mayo-Wilson E, Li T, **Fusco N**, Bertizzolo L, Canner JK, Cowley T, et al. *Cherry-picking by trialists and meta-analysts can drive conclusions about intervention efficacy*. Journal of Clinical Epidemiology. 2017.

Part II

Teaching Experience

2016-2017 *Systematic Reviews and Meta-Analysis* (Lead Teaching Assistant) (two times)
Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
Faculty – Drs. Kay Dickersin and Tianjing Li

2015 *Systematic Reviews and Meta-Analysis* (Teaching Assistant)
Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
Faculty – Drs. Kay Dickersin and Tianjing Li

2013-2014 *Introduction to Clinical Trials* (Teaching Assistant) (two times)
Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
Faculty – Drs. Janet Holbrook and Lea Drye

2014 *Principles of Epidemiology* (Teaching Assistant)
Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
Faculty – Drs. David Celentano and Elizabeth Platz

Presentations

Poster Presentations:

1. **Fusco N**, Mayo-Wilson E, Li T, Dickersin K. Evidence that multiplicity in outcome definitions could introduce selective outcome reporting. Poster presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
2. **Fusco N**, Dickersin K, Scherer RW, Bertizzolo L, Saldanha I, Vedula SS, Li T, Mayo-Wilson E. The pros and cons of including abstracts in systematic reviews: findings from the Multiple Data Sources Study (MUDS). Poster presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
3. **Fusco N**, Le J, Rouse B, Arno A, Elliott J, Li T, Dickersin K. Feedback on Covidence by systematic reviewers. Poster presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
4. **Fusco N**, Saldanha I, Gresham G, Li T. Lack of originality in non-Cochrane systematic reviews. Poster presented at: Evidence-informed public health: Opportunities and challenges. 22nd annual Cochrane Colloquium; Sept 21-25, 2014; Hyderabad, India.

Oral Presentations:

1. **Fusco N**, Mayo-Wilson E, Li T, Dickersin K. Do multiple data sources about a single trial agree on risk of bias and PICO (participant, intervention, comparator, outcome) information? Presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
2. Li T, Hong H, **Fusco N**, Mayo-Wilson E, Dickersin K. Too much data from too many sources: what is the best estimate of the treatment effect? Presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
3. Mayo-Wilson E, **Fusco N**, Ehmsen J, Gresham G, Heyward J, Hutfless S, Li T, Lock D, Suarez-Cuervo S, Dickersin K. Wasted results: Multiplicity in outcome definitions is a mechanism for reporting bias. Presented at: Increasing value and reducing waste in biomedical research conference; 1st REWARD/EQUATOR conference; Sept 28-30, 2015; Edinburgh, UK.
4. Dickersin K, Mayo-Wilson E, **Fusco N**, Li T. What are the consequences for systematic reviews when we demand "open science"? Findings from the Multiple Sources of Data (MUDS) Research Study. Presented at: Society for Research Synthesis and Methodology Annual Meeting; July 11-13, 2016; Florence, Italy.
5. Li T, Hong H, **Fusco N**, Mayo-Wilson E, Dickersin K. Too much data from too many sources: what is the best estimate of the treatment effect? Presented at: Society for Research Synthesis and Methodology Annual Meeting; July 11-13, 2016; Florence, Italy.
6. **Fusco N**, Saldanha I, Williamson P, Kirkham J, Brookes S, Dickersin K. Outcomes in Trials and Systematic Reviews: Why we should be paying more attention. Presented at 4th International Clinical Trials Methodology Conference, held jointly with the 38th annual Society for Clinical Trials Meeting; May 8-10, 2017; Liverpool, UK.

Workshops:

1. **Fusco N**, Li T, Dickersin K, Gresham G, Mayo-Wilson E. Navigating the clinical study report (CSR): a road map to the data abstraction of CSRs for systematic reviews. Presented at: Challenges to evidence-based health care and Cochrane. 24th annual Cochrane Colloquium; Oct 23-27, 2016; Seoul, South Korea.
2. **Fusco N**, Scherer R, Dickersin K, Gresham G, Mayo-Wilson E, Li T. Navigating the clinical study report (CSR): a road map to the data abstraction of CSRs for systematic reviews. Presented at: Filtering the information overload for better decisions. 23rd annual Cochrane Colloquium; Oct 3-7, 2015; Vienna, Austria.

Additional Information

Date of Birth

April 1, 1987

Place of Birth

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Personal Statement of Research Interests

My research expertise is drawn from my experience and rigorous training in epidemiology and biostatistics. I am interested specifically in adverse events research, reporting bias, and outcome selection. More broadly, I'm interested in developing and improving methodology for randomized controlled trials and systematic reviews.

Keywords

Adverse events, safety, harms, randomized controlled trials, systematic reviews, meta-analysis, evidence-based healthcare, reporting bias, neuropathic pain, bipolar depression